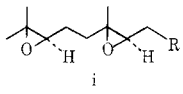

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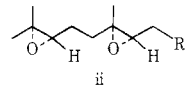
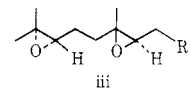
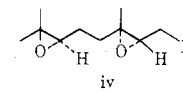


ii

form the same 11*R*,14*S* cis isomer *via* structures X and Y, respectively. Trans isomer 11*R*,14*R* would be formed by operation of scheme X from diepoxide iii or by scheme Y from diepoxide iv. Formation of the 11*S*,14*S* trans isomer could not occur by a concerted reaction.



iii



iv

(28) For experimental details, see previous articles of this series.
(29) W. Herz and G. Högenauer, *J. Org. Chem.*, **27**, 905 (1962).
(30) Apparently initial oxidation of one of the hydroxyl groups results in deactivation of MnO_2.

New Guaianolides from *Liatris* Species[1]

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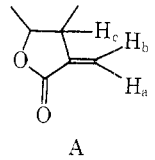
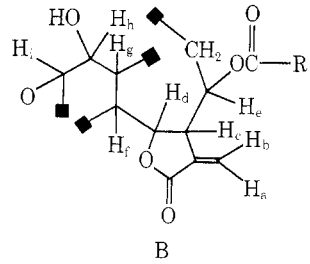
Five closely related guaianolides have been isolated from three *Liatris* species. *L. graminifolia* (Walt.) Kuntze gave graminiliatrin (**1a**), deoxygraminiliatrin (**2a**), and graminichlorin (**3**). *L. spicata* (L.) Kuntze yielded spicatin (**2b**) and *L. pycnostachya* (Michx.) Kuntze furnished spicatin and epoxyspicatin (**1c**). Euparin was also found. Structures and stereochemistries of the new lactones were determined by chemical transformations, correlations, and physical techniques.

Since previously investigated representatives of the genus *Liatris* (tribe Eupatorieae, Compositae) have been found to elaborate cytotoxic and antileukemic sesquiterpene lactones of the germacranolide type,[2-4] it was of interest to examine other accessible *Liatris* species. In the present article, we report isolation and structure determination of five new closely related guaianolides from *Liatris graminifolia* (Walt.) Kuntze, *L. pycnostachya* (Michx.) Kuntze, and *L. spicata* (L.) Kuntze. Three of these, graminiliatrin (**1a**), deoxygraminiliatrin (**2a**), and graminichlorin (**3**), were isolated from *L. graminifolia;* two others, spicatin and epoxyspicatin, for which structures **2b** and **1c** are preferred to structures **2d** and **1d,** came from *L. pycnostachya.* Spicatin was also the main lactone constituent of *L. spicata.* In addition the benzofuran derivative euparin (**14**) was isolated from *L. graminifolia* and *L. spicata.*[5]

Since none of the new lactones could be induced to crystallize, purification had to depend on chromatography monitored by spectroscopic techniques. Graminiliatrin (**1a**), $C_{22}H_{26}O_9$ (high-resolution mass spectrum, $[\alpha]^{22}D$ −48.6°, the major lactone constituent of *L. graminifolia,* was, like the other four lactones, a conjugated γ-lactone (ir bands at 1770 and 1660 cm^{-1}) of the type represented by partial formula A because of the presence in the nmr spectrum of the characteristic signals of H_a and H_b at 6.31 and 5.53 ppm. Expansion of A to partial structure B, where the symbol ■ represents quaternary carbon, was made possible



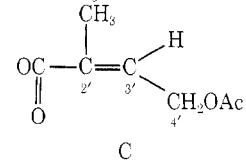
A



B

by spin-decoupling experiments.[8] Thus, H_c (multiplet near 3.6 ppm) was coupled to H_d (doublet of doublets near 4.7 ppm) and H_e (d of d of d near 5.6 ppm) as well as to H_a and H_b; the relative shifts of H_d and H_e indicated that H_d represented the proton under the lactone ether oxygen,[9] whereas H_e was attached to a carbon atom carrying one of the two ester functions whose presence was suggested by ir bands at 1740 and 1725 cm^{-1}. The two other protons responsible for the appearance of the H_e signal were visible in the 270-MHz spectrum as the AB part of an ABX system, geminally coupled ($|J|$ = 15 Hz) and apparently adjacent to fully substituted carbon. H_d was also coupled to H_f (d of d at 2.50 ppm); H_f was in turn coupled to H_g (d of d at 1.76 ppm) which was coupled to a broad doublet at 4.35 ppm (H_h). That H_h was geminal to the hydroxyl group evidenced in the ir spectrum of graminiliatrin was demonstrated by the sharpening of its signal of D_2O exchange and by the paramagnetic shift to 5.36 ppm which accompanied acetylation of graminiliatrin to **1b.** Lastly, the additional broadening of the H_h signal could be traced to coupling to H_i at 3.33 ppm; the chemical shift of the latter suggested that it represented a proton on carbon carrying an ethereal oxygen atom.

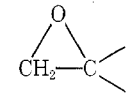
The pmr spectrum of graminiliatrin also revealed the presence of a vinyl methyl multiplet at 1.84 ppm, a vinyl proton multiplet at 6.02 ppm, a two-proton multiplet at 4.88 ppm, and an acetate methyl at 2.07 ppm. Irradiation at 6.02 ppm simplified the multiplets at1.84 and 4.88 ppm, thus indicating the presence of partial structure C^{10} which

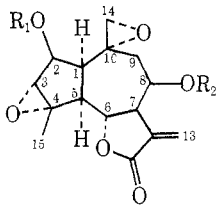


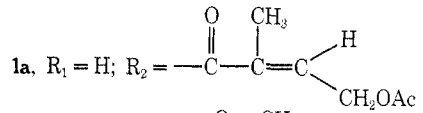
C

would represent the ester function geminal to H_e and would account for the ir bands at 1740 and 1725 cm^{-1}. This deduction was strengthened by the presence in the high-resolution mass spectrum of peaks at *m/e* 158 ($C_7H_{10}O_4$), 140 ($C_7H_8O_3$), and 99 ($C_5H_7O_2$).

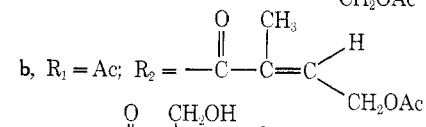
Two additional features of the pmr spectrum remain to be mentioned. One was a three-proton singlet at 1.67 ppm ascribable to a methyl group on carbon carrying oxygen. The second was a two-proton AB system centered at 2.68 ppm characteristic of the grouping



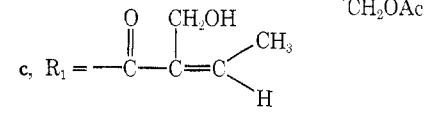




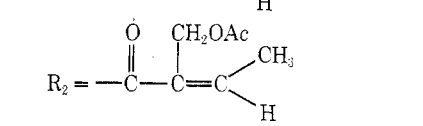
1a, $R_1 = H$; $R_2 =$



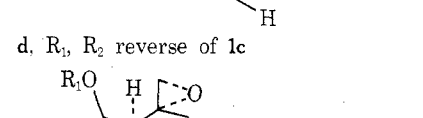
b, $R_1 = Ac$; $R_2 =$



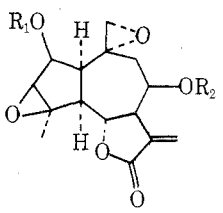
c, $R_1 =$

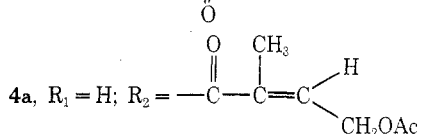


$R_2 =$

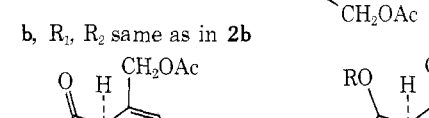


d, R_1, R_2 reverse of **1c**

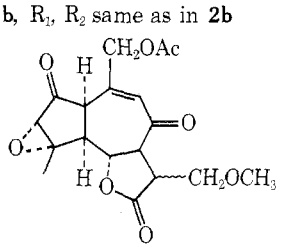




4a, $R_1 = H$; $R_2 =$



b, R_1, R_2 same as in **2b**



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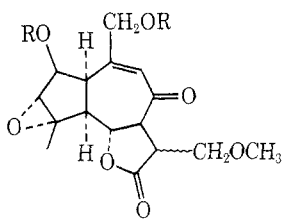
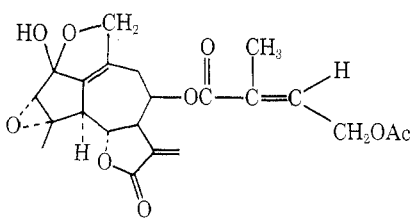


9a, R = H
b, R = Ac



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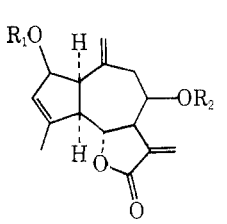
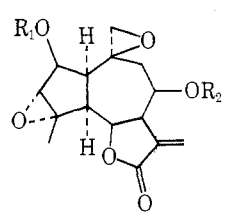
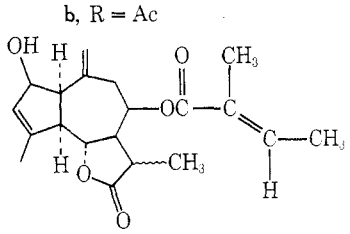


11, R_1, R_2 same as in **2b**



12, R_1, R_2 same as in **2b**



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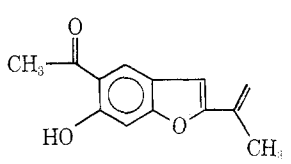

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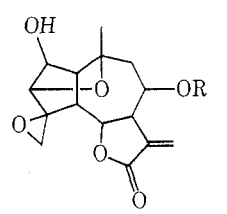

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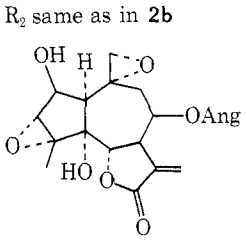

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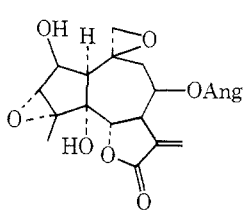

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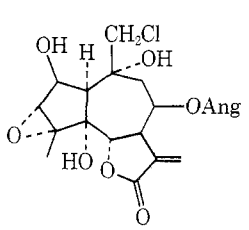


18

These features can be combined with partial structure B in two and only two ways, **1a** (exclusive of stereochemistry) or **15**, to satisfy the empirical formula and the spectral data. Either formula is biogenetically plausible, but only **1a** is compatible with the transformations and correlations which will be described in the sequel.

Treatment of **1a** with K_2CO_3–MeOH at room temperature resulted in conversion to crystalline **5a** by loss of the

seven-carbon ester function and addition of the elements of methanol to the conjugated exocyclic methylene function, as evidenced in the pmr spectrum (Table I) and by mass spectrometry. Acetylation of **5a** gave the diacetate **5b**; comparison of the chemical shifts of H_d and H_e in the course of the transformation **1a** → **5a** → **5b** confirmed the correctness of the original assignment of H_d to H-6 and H_e to H-8 and demonstrated that hydrolysis had occurred without lactone ring reorientation.

Jones oxidation of **5a** afforded a mixture which was separated chromatographically. The major component, $C_{16}H_{18}O_7$, was the α,β-unsaturated ketone **7** (λ_{max} 235 nm, new ir band at 1670 cm^{-1}) whose pmr spectrum (Table I) no longer contained the signal of H-2 and the ABX system of H-8, H-9a, and H-9b, but exhibited instead a new ABX system involving H-8 as a vinyl multiplet 6.06 ppm, clearly part of the conjugated ketone chromophore, coupled to two protons at 4.94 and 4.59 ppm assignable to H-14a and H-14b. Formation of this system as the result of β elimination definitely ruled out formula **15** for graminiliatrin. Since the ir spectrum of the oxidation product exhibited only a very weak cyclopentanone frequency at 1735 cm^{-1}, preponderance of the hemiketal structure **7** was assumed, but conversion to the acetate resulted in regeneration of the ketone structure **8** (new ir bands at 1750 and 1735 cm^{-1}, downfield shift of H-3).

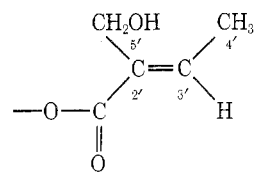
The minor component of the oxidation mixture, $C_{16}H_{20}O_7$, was recognized as **9a** on the basis of its spectral properties and could be converted to the diacetate **9b** whose ir, pmr, and mass spectra were in complete agreement with the assigned structure. Lastly, Jones oxidation of graminiliatrin itself gave a substance **10** by β elimination toward C-1, a transformation which confirms the relationship of the functional groups on C-14, C-10, and C-2 deduced previously. The pmr spectrum of **10** (Table I) was similar to that of **1a** except for the shift of H-14a and H-14b to lower field, the disappearance of H-1 and H-2, and some simplification in the signals of H-7 and H-8. Apparently the introduction of the 1,10 double bond has the result of reducing $J_{7,8}$ to a very small value. Molecular models based on the stereochemistry deduced for graminiliatrin (*vide infra*) demonstrate that this should actually be the case.

The second sesquiterpene lactone from *L. graminifolia*, deoxygraminiliatrin, $C_{22}H_{26}O_8$, had one less oxygen atom than graminiliatrin and appeared to possess an isolated double bond (ir band at 1610 cm^{-1}). Comparison of its pmr spectrum with that of **1a** showed the following differences (Table I). The H-3 singlet of **1a** at 3.33 ppm was replaced by a multiplet at 5.68 ppm which was coupled to a broad vinyl methyl singlet at 1.94 ppm, the latter having replaced the sharp three-proton singlet of **1a** at 1.67 ppm, and the H-2 signal had experienced a downfield shift to 4.6 ppm.

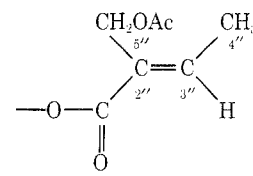
On this basis it appeared obvious that deoxygraminiliatrin had a 3,4-double bond instead of a 3,4-epoxide. Confirmation for its formation as **2a** was provided by treatment of deoxygraminiliatrin with *m*-chloroperbenzoic acid which resulted in formation of two products with opposite stereochemistry at C-3, C-4. The major isomer was identical with graminiliatrin. The pmr spectrum of the minor product **4a** (Table I) differed from that of **1a** only in the value of $J_{2,3}$ and in the chemical shifts of H-14.

The third lactone from *L. graminifolia* was named graminichlorin because of its molecular formula which suggested that it was an HCl adduct of **1a**.[11] The pmr spectrum (Table I) was in complete agreement with its formulation as **3**, apart from the stereochemistry. Treatment of graminichlorin with acid-washed alumina or silica gel resulted in essentially quantitative conversion to **1a**, thus confirming this conclusion.

Spicatin, $C_{27}H_{32}O_{10}$, $[\alpha]^{22}$ −146°, the main lactone constituent of *L. spicata* and *L. pycnostachya*, contained the *cis*-sarracinoyl and *cis*-acetylsarracinoyl residues D and E. This was evident from the pmr spectrum which exhibited two sets of quartets near 7 ppm characteristic of H-3′ and H-3″ in a *cis*-sarracenoyl unit,[4,15] each coupled to a separate vinyl methyl doublet near 1.9 ppm (H-4′ and H-4″), a broadened two-proton singlet (H-5″) at 4.2, a two-proton AB system centered near 4.8 ppm (H-5′), and an acetate singlet. High-resolution mass spectra which contained diagnostic peaks corresponding to $C_7H_9O_3$, $C_5H_7O_2$, and C_5H_5O or to ions resulting from loss of such fragments supported this assignment, as did conversion of spicatin to its monoacetate **2c** which sported two identical ester side chains.



D



E

While analysis of the pmr spectra of spicatin, which was isolated prior to the discovery of graminiliatrin, and its derivatives (Table I) independently led to its formulation as **2b**, the procedure, because of the superposition of signals, was very involved and will not be detailed here. Instead we describe the eventual correlation of spicatin with deoxygraminiliatrin (**2a**) which achieved the same result. Hydrolysis of **2a** with K_2CO_3–MeOH gave a gummy diol lactone **6** without reorientation of the lactone ring (pmr spectrum, Table I), which was converted for characterization purposes to the previously described crystalline epoxide **5a** and its acetate **5b**.[16] Hydrolysis of spicin under identical conditions was more complicated; the material formed in largest amount, again without reorientation of the lactone ring, was identical with **6** and was again converted to **5a** and **5b** identical with authentic samples.

Epoxidation of spicatin gave epoxyspicatin (**1c**), identical with a minor constituent of *L. picnostachya*. The pmr spectrum of this material (Table I) was very similar to that of acetylgraminiliatrin (**1b**), except for the difference in ester functions on C-2 and C-8; hence the epoxide ring of **1c** has the same stereochemistry as that of graminiliatrin (**1a**).

There remained the problem of deciding between structure **2b** for spicatin and the alternative **2d** in which the location of the two ester side chains is reversed. Numerous attempts to hydrolyze one of the two ester functions selectively in order to settle this question were abortive; however, a tentative solution to the problem was provided in the course of work aimed at deoxygenation of spicatin.

Treatment of spicatin with zinc–copper couple in ethanol gave, as expected,[12,17] a substance **11** whose pmr spectrum (Table I), by exhibiting the H-1 signal as a deshielded doublet of doublets at 3.47 ppm, was useful in deducing the carbon skeleton of spicatin by pmr spectrometry. Epoxidation of **11** gave two isomers, the first of which was identical with **1c** which had been obtained earlier by direct epoxidation of spicatin. The second product was provisionally assigned formula **12** rather than **4b** because of the appearance and chemical shift of the H-3 and H-14 signals (*vide supra*).

When the reduction of spicatin with zinc–copper couple

Table I
Pmr Spectra of Graminiliatrin and Derivatives[a]

Compd	H-1	H-2	H-3	H-5	H-6	H-7	H-8	H-9	H-13	H-14[b]	H-15[c]	Miscellaneous
1a[d]	1.76 dd (4.5, 7.4)	4.35 d br (4.5)	3.33 br	2.50 dd (7.4, 11)	4.83 dd (11, 8)	3.55 dddd (8, 4, 3.5, 3.2)	5.60 ddd (4, 8.5, 7)	2.13 d (15, 7) 2.90 dd (15, 8.5)	6.31 d (3.5) 5.53 d (3.2)	2.70[e]	1.67	6.02 m (H − 3′), 4.88 m (H − 4′)[e], 1.84 m (H − 5′),[c] 2.07 (Ac)
1b	*f*	5.36 d br (4.5)	3.38 br	*f*	4.72 dd (11, 8)	3.56 m	5.59	*f*	6.37 d (3.5) 5.56 d (3.2)	2.69[e]	1.68	6.02 m (H − 3′), 4.89 m (H − 4′),[e] 1.83 m (H − 5′),[c] 2.06, 2.10 (Ac)
1c	*f, g*	5.37 d br (4.5)	3.40 br	2.58 dd (8, 11)	4.74 dd (11, 8)	3.56 dddd (8, 3.9, 3.6, 3.2)	5.63 td (8, 8, 3.9)	2.23 dd[h] (15, 8)	6.31 d (3.6) 5.58 d (3.1)	2.68[e]	1.68	6.90 q (7, H − 3′), 1.92 d (7, H − 4′),[c] 4.33 br (H − 5′),[e] 7.08 q (7, H − 3″), 1.97 d (7, H − 4″),[c] 4.89 (H − 5″),[e] 2.11 (Ac)
2a	*f*	4.60 d br (4.5)	5.68 m	*f*	4.70 dd (11, 8)	3.50 m	5.53 m	*f*	6.27 d (3.5) 5.50 d (3.2)	2.73[e]	1.94 br	5.93 m (H − 3′), 4.89 m (H − 4′),[e] 1.83 m (H − 5′),[c] 2.02 (Ac)
2b[i]	~1.58	*j*	*j*	2.19 dd (9, 11)	4.60 dd (11, 8)	3.56 dddd (8, 3.9, 3.6, 3.2)	5.51 td (8, 8, 3.9)	2.18[k]	6.23 d (3.6) 5.21 d (3.1)	2.22[e]	1.68 br	6.81 q (7, H − 3′), 1.39 d (7, H − 4′),[c] 4.25 br (H − 5′),[e] 6.94 q (7, H − 3″), 1.50 d (7, H − 4′),[c] 4.76 (H − 5″),[e] 1.83 (Ac)
2c	*f*	*l*	*l*	2.82 dd (9, 11)	4.64 dd (11, 8)	3.60 m	*e*	2.26 m	6.21 d (3.6) 5.21 d[e] (3.1)	2.74[e]	2.02 br	7.06 q (7, H − 3′, H − 3″),[b] 1.93 d (7, H − 4′, H − 4″),[m] 4.85 (H − 5′, H − 5″),[e] 2.02, 2.02 (Ac)
3	*f*	4.29 d br (4.5)	3.31 br	*f*	4.81 dd (11, 8)	4.03 m	5.62	*f*	6.27 d (3.5) 5.45 d (3.2)	3.61 d (12) 3.78 d (12)	1.71	6.03 m (H − 3′), 4.88 m (H − 4′),[e] 1.85 m (H − 5′),[c] 2.08 (Ac)
4a	*f*	4.50 dd (4.5, 1.5)	3.49 d (1.5)	*f*	4.91 dd (11, 8)	3.33 m	5.61	*f*	6.35 d (3.5) 5.59 d (3.2)	3.36 d (4.5) 2.77 d (4.5)	1.60	6.06 m (H − 3′), 4.91 m (H − 4′),[e] 1.87 m (H − 5′),[c] 2.09 (Ac)
5a[o]	*f*	4.13 t (4.5)[p]	3.22 br	*f*	4.55 dd (11, 8.5)	*f*	3.77 m	*f*	3.55 m	2.60[e]	1.44	3.25 (OMe), 4.96 d (OH) 5.46 d (OH)
5[b]	*f*	5.30 d (4.5)	3.30	*f*	4.61 dd (11, 8.5)	*f*	5.18 m	*f*	3.61 m	2.60[e]	1.55	3.33 (OMe), 2.08, 2.03 (Ac)
7	*f*		3.47	*f*	4.26 dd (11, 8.5)	*f*		6.06 br[q]	3.58 m	4.94[r] 4.59[r]	1.55	3.33 (OMe)
8	*f*		3.93	*f*	4.27 dd (11, 8.5)	*f*		6.08 br[q]	3.60 m	4.99[r] 4.69[r]	1.54	3.33 (OMe), 2.10 (Ac)
9a[n]	*f*	4.22 t (4.5)[p]	3.47 br	*f*	4.55 t (10)	*f*		6.27 br[q]	3.55 m	4.05 m[e]	1.55	3.22 (OMe), 5.38 d, 5.33 m (OH)

9b	*f*	5.49 d (4.5)	*f*	*f*	4.36 t (10)	*f*		6.27 br[a]	3.55 m	4.60 m[e]	1.70	3.33 (OMe), 2.13, 1.95 (Ac)	
10		3.42	*f*		4.17 t (10)	3.16 m	5.72 d br (6)	*f*	6.22 d (3.5)	4.66 br 4.25 br	1.80	6.04 m (H − 3′), 4.81 m (H − 4′),[e] 1.80 m (H − 5′),[c] 2.04 (Ac)	
									5.47 d (3.0)				
11	3.47 dd (6.8, 9)	*l*	*l*	*f*	4.63 dd (10.5, 8.5)	3.23 m	*l*	2.39 m	6.26 d (3.6)	5.03 br	1.97 br	6.89 q (7, H − 3′), 1.93 d (H − 4′),[c] 4.33 br (H − 5′),[c] 7.09 q (7, H − 3″), 1.99[d] (7, H − 4′),[c] 4.90 (H − 5″),[e] 2.02 (Ac)	
									5.54 d (3.1)				
12	*f*	5.42 d br (5)	3.47 br	*f*	4.76 dd (11, 8)	3.62 m	5.63 m	*f*	6.32 d (3.6)	2.70[e]	1.71	6.88 q (7, H − 3′), 1.95 d (7, H − 4′),[c] 4.35 br (H − 5′),[e] 7.09 q (7, H − 3″), 1.93 d (7, H − 4″),[c] 4.87 (H − 5″),[e] 2.15 (Ac)	
									5.60 d (3.1)				
13	3.15 dd (5.5, 8)	4.74 d br (5.5)	5.74 m	*f*	4.54 dd (9.5, 10)	2.14 ddd (10, 3.2, 12)	5.22 dt (3.2, 8, 8)	2.7 m[e]	1.24 d (7)[e]	5.08 m	1.97 br	2.53 q[d] (7, 12, H − 11), 6.85 m (H − 3′), 1.83 m,[e] 1.97 m (H − 4′, H − 5′)[e]	

[a] Run at 90 MHz in $CDCl_3$ solution except where indicated, using TMS as internal standard. Values are in parts per million. Multiplicities are indicated by the usual symbols: d, doublet; t, triplet; q, quartet; br, broadened singlet; m, multiplet whose center is given. Unmarked signals are singlets. Figures in parentheses are line separations or coupling constants in hertz. [b] Intensity two protons. [c] Intensity three protons. [d] Run at 270 MHz, spin decoupled. [e] Center of AB, frequently broad singlet. [f] Obscured by superposition of signals. [g] Visible in C_6D_6 solution (decoupled) as 1.73 dd (5, 9). [h] Second proton obscured. In C_6D_6, center of AB part of ABX, superimposed on H-5 signal at 2.13 ppm. [i] In C_6D_6, spin decoupled. [j] In two-proton multiplet at 5.44 ppm. [k] Center of AB part of ABX, $J_{AX} \pm J_{BX} = 9$, $J_{AB} = 15$ Hz. [l] In four-proton multiplet near 5.6 ppm. [m] Intensity six protons. [n] Intensity four protons. [o] In DMSO-d_6. [p] Collapses to doublet on D_2O exchange. [q] X of ABX ($J_{AX} = 2$; $J_{BX} = 1.5$; $J_{AB} = 14$ Hz). [r] A and B of ABX.

was carried out in the presence of hydrochloric acid, the only product which could be characterized satisfactorily was the monoester **13.** That reduction of the conjugated lactone system had accompanied deoxygenation of the epoxide function was evident from the pmr spectrum (Table I), as was the hydrolytic loss of the ester side chain on C-2. The remaining ester side chain on C-8 had suffered hydrogenolysis to a tigloyl residue (H-3′ multiplet at 6.85, two vinyl methyl multiplets at 1.83 and 1.97 ppm), a conclusion confirmed by the mass spectrum which exhibited the base peak at *m/e* 83.0436 (C_5H_7O). Since acetate is a much better leaving group than OH, we suggest that the formation of **13** favors formula **2b** for spicatin rather than formula **2d.** Nevertheless, further evidence on this point is clearly desirable and is currently being sought.

The stereochemistry of the substances described in this report has been deduced as follows. If the usual assumption is made that the C-7 side chain is β and equatorial as in all sesquiterpene lactones of authenticated stereochemistry, the values of $J_{5,6}$ and $J_{6,7}$ given in Table I (generally 11 and 8 Hz, respectively) require that H-5 be trans to H-6 and α and that H-6 be trans to H-7 and β, *i.e.*, that the lactone ring be trans fused. This conclusion is reinforced by the magnitude of $J_{7,13a}$ and $J_{7,13b}$ (>3 Hz) which according to Samek's rule[18] indicates presence of a *trans*-lactone.[19] The relatively small value of $J_{7,8}$ (~4 Hz) then requires that H-8 be equatorial and α.

The relative stereochemistry in the five-membered ring was established as follows. H-3 appears as a slightly broadened singlet in the pmr spectra of all epoxides except **4a** which is stereoisomeric at C-3 and C-4. The molecular models show that with the epoxide α and the 2-hydroxyl group β as in **1a,** the dihedral angle subtended by H-2 and H-3 is 90°, whereas with the epoxide β and the hydroxyl β, as suggested for **4a,** the dihedral angle is 60°, thus accounting for the differences in the coupling constants actually observed. The values of $J_{1,2}$ (4.5 Hz) and $J_{1,5}$ (7.4 Hz) then require α orientation for H-1 and H-5; the latter conclusion has been reached independently (see previous paragraph) by considering the coupling constants in the seven-membered ring. Hence the two rings are cis fused.

The stereochemistry at C-10 then follows from the effect of the β-oriented epoxide function of **4a** on the chemical shift of H-14. The observed downfield shift (see Table I) can be rationalized only if the methylene group attached to C-10 is β oriented. A similar conclusion is reached when the appearance and chemical shifts of H-1, H-9, and H-14 in the pmr spectrum of **1a** are compared with the corresponding signals in the pmr spectra of eupatoroxin (**16**) and 10-epieupatoroxin (**17**)[12] whose relative and absolute stereochemistry is known. Lastly, comparison of the pmr spectra of graminichlorin (**3**) and eupachloroxin (**18**) shows that the C-10 substituents of both compounds are similarly oriented. In both instances, H-7 exhibits a downfield shift of about 0.5 ppm. This indicates that the hydroxyl group on C-10 is in close proximity to H-7 which is possible only if the hydroxyl group of **3** (like that of **18**) and hence the epoxide function of **1a** are α-oriented.[23]

A consequence of the cis-1,5,trans-6,7 stereochemistry deduced for the new lactones is the proximity, apparent from models, of H-6 to one of the protons on H-9 which should be reflected in a relatively strong NOE. Indeed, irradiation at a frequency corresponding to the center of the H-9 AB system in spicatin (C_6D_6 solution) produced a 27.1% enhancement in the integrated intensity of H-6. As expected on the basis of the model, there were no NOE's between H-1 on the one hand and H-2, H-5, and H-7 on the other.

Experimental Section[24]

Extraction of *Liatris graminifolia.* Above ground parts of *Liatris graminifolia* (Walt.) Kuntze, wt 16.2 kg, collected by R. Lazor on Sept 22, 1971, 12 km east of the junction of U.S. 319 and State Road 155, Thomas Co., Georgia (Lazor no. 5585 on deposit in herbarium of Florida State University) was extracted with chloroform and worked up in the usual manner.[25] The crude gum, wt 120 g, was chromatographed over 1.25 kg of silicic acid (Mallinckrodt 10 mesh), 1-l. fractions being collected. Fractions 1–2 (benzene) gave 100 mg of a yellow solid which melted at 120–121° after recrystallization from isopropyl ether–hexane and was identified as euparin by comparison of its ir and nmr spectra with those of an authentic sample, mmp 120–121°.[26]

Fractions 3–10 (benzene) gave 1.2 g of gummy graminichlorin (**3**) which was homogeneous on tlc: $[\alpha]^{22}$D −36.0° (*c* 1.25, $CHCl_3$); uv end absorption; ir bands at 3460 (hydroxyl), 1770 (γ-lactone), 1740 (acetate), 1725 (conjugated ester), 1650 (C=C), 1250, 1030, 980, 950, and 830 cm^{-1}; low-resolution mass spectrum *m/e* 470 and 472 (3:1, M^+, $C_{22}H_{27}O_9Cl$), 452 and 454 (3:1, M −18, $C_{22}H_{25}O_8Cl$); other major peaks were at 392 (M − 18 − 60), 375, 278, 277, 276, 275, 259, 258, 257, 150, 140, and 99 (base peak).

Anal. Calcd for $C_{22}H_{27}ClO_9$: C, 56.17; H, 5.75; Cl, 7.45. Found: C, 56.18; H, 5.84; Cl, 7.19.

Fractions 11–15 (benzene) gave 2 g of crude gummy deoxygraminiliatrin (**2a**) which was purified by preparative tlc on silica gel (solvent benzene–ethyl acetate, 2:1): $[\alpha]^{22}$D −48.5° (*c* 0.735, $CHCl_3$); ir bands at 3460 (hydroxyl), 1770, 1660 (conjugated γ-lactone), 1725 (conjugated ester), 1610, 1240, 1020, 925, and 860 cm^{-1}; low-resolution mass spectrum *m/e* 418 (M^+), 358 (M − 60), 277, 276 (M − $C_7H_{10}O_3$), 261, 260 (M − $C_7H_{10}O_4$), 259, 243, 242 (M − $C_7H_{10}O_4$ − H_2O), and 99 (base peak).

Anal. Calcd for $C_{22}H_{26}O_8$: C, 63.15; H, 6.26; O, 30.59. Found: C, 63.43; H, 6.20; O, 30.67.

Elution with benzene–$CHCl_3$ (10:1 and 1:1, fractions 16–41) gave the major component which was further purified by chromatography over 600 g of silica gel to give 40 g of colorless graminiliatrin (**1a**) which could not be induced to crystallize: $[\alpha]^{22}$D −48.6° (*c* 1.0, $CHCl_3$); CD curve λ_{max} 260 nm; $[\theta]$ −545; uv λ_{max} 212 (ε 15,600); ir bands at 3460 (hydroxyl), 1770, 1660 (conjugated γ-lactone), 1740 (acetate), 1725 (conjugated ester), 1250, 1020, 970, 920, and 835 cm^{-1}; high-resolution mass spectrum *m/e* (composition, per cent) 434 (M^+, $C_{22}H_{26}O_9$, 0.2), 392 (M − 42, $C_{20}H_{24}O_8$, 1.2), 374 (M − 60, $C_{20}H_{22}O_7$, 0.4), 277 (M − $C_7H_9O_4$, $C_{15}H_{17}O_5$, 2.8), 276 (M − $C_7H_1O_4$, $C_{15}H_{16}O_5$, 2.0), 275 (M − $C_7H_{11}O_4$, $C_{15}H_{15}O5$, 0.9), 259 (M − 157 − 18, $C_{15}H_{15}O_4$, 5.4), 258 (M − 158 − 18, $C_{15}H_{14}O_4$, 4.8), 158 ($C_7H_{10}O_4$, 5.6), 140 ($C_7H_8O_3$, 8.7), 99 ($C_5H_7O_2$, 100).

Anal. Calcd for $C_{22}H_{26}O_9$: mol wt, 434.1575. Found: mol wt (ms), 434.1546.

Acetylation of 0.1 g of **1a** with 1 ml of acetic anhydride in 0.5 ml of pyridine at room temperature overnight gave, after the usual work-up, the acetate **1b** as a gum: yield 0.095 g; $[\alpha]^{22}$D −55.3° (*c* 0.11, $CHCl_3$); ir bands at 1760, 1740, 1725, 1650, 1240, 1025, 970, 920, 870, and 830 cm^{-1}; high-resolution mass spectrum *m/e* (composition, per cent) 476 (M^+, $C_{24}H_{28}O_{10}$, 2–3), 433 (M − 43, $C_{22}H_{25}O_9$, 1.2), 417 (M − 59, $C_{22}H_{25}O_8$, 37.5), 375 (M − 59 − 42, $C_{20}H_{23}O_7$, 1.4), 374 (M − 59 − 43, $C_{20}H_{22}O_7$, 4.8), 373 (M − 60 − 43, $C_{20}H_{21}O_7$, 4.3), 357 ($C_{20}H_{21}O_6$, 2.4), 356 ($C_{20}H_{20}O_6$, 3), 277 ($C_{15}H_{17}O_5$, 8.5), 276 ($C_{15}H_{16}O_5$, 10), 259 ($C_{15}H_{15}O_4$, 6.1), 258 ($C_{15}H_{14}O_4$, 44.5), 159 ($C_7H_{11}O_4$, 0.9), 158 ($C_7H_{10}O_4$, 3.4), 141 ($C_7H_9O_{31}$, 3.6), 140 ($C_7H_8O_3$, 16.3), 99 ($C_5H_7O_2$, 100).

Anal. Calcd for $C_{24}H_{28}O_{10}$: mol wt, 476.1680. Found: mol wt (ms), 476.1673.

Extraction of *Liatris spicata.* Above ground parts of *Liatris spicata* (L.) Kuntze, wt 22.2 kg, collected by Dr. R. K. Godfrey on Sept 18, 1971 in the vicinity of Tallahassee (Godfrey no. 70894) was extracted with $CHCl_3$ and worked up as usual. The crude gum, wt 70 g, was chromatographed over 1 kg of silicic acid, 1-l. fractions being collected in the following order: 1–28 (benzene), 29–40 (benzene–$CHCl_3$, 4:1), 41–55 (benzene–$CHCl_3$, 1.4), 71–100 ($CHCl_3$), 101–110 ($CHCl_3$–MeOH, 99:1), 111–120 ($CHCl_3$–MeOH, 19:1), 121–125 (MeOH). Fractions 2 and 3, wt 4.2 g, were combined and recrystallized to give euparin, mp 120°, identical with an authentic sample. Fractions 4–54, total wt 4.5 g, contained mixtures. Fractions 55–80, wt 20 g, which showed a major spot on tlc were combined and rechromatographed over 1.3 kg of silica gel (Grace 60–200 mesh), using initially petroleum ether–acetone–ether saturated with water (4:1:1) and then increasing polarity of the solvent system. The central fractions which showed single spots on tlc were combined to give 8.48 g of spicatin (**2b**) as a resin which could not be induced to crystallize. It was further purified by rechromatography over 80 g of cellulose (Whatman standard grade), using the previous solvent system and then had $[\alpha]^{22}_{Hg}$ −146° (*c* 0.20, $CHCl_3$); CD curve λ_{max} 265 nm ($[\theta]$ −900); ir bands at 3510 (OH), 1778, 1652 (conjugated γ-lactone), 1715 (strong, conjugated esters); chemical ionization mass spectrum *m/e* 517 (MH^+, 0.5), 499 (MH^+ − 18, 0.2), 439 (MH^+ − 18 − 60, 2.3), 399 (MH^+ − 118, 7); high-resolution mass spectrum *m/e* (composition, per cent) 516 (M^+, 0.2), 498 ($C_{27}H_{30}O_9$, 0.05), 456 ($C_{25}H_{28}O_8$, 0.2), 420 ($C_{25}H_{24}O_6$, 0.7), 359 ($C_{20}H_{23}O_6$, 0.9), 342 ($C_{20}H_{22}O_5$, 1.0), 312 ($C_{19}H_{20}O_4$, 1.4), 99 ($C_5H_7O_2$, 100), and 81 (C_5H_5O, 48).

Anal. Calcd for $C_{27}H_{32}O_{10}$: C, 62.78; H, 6.24; O, 30.97; mol wt, 516.1992. Found: C, 62.41; H, 6.65; O, 30.40; mol wt (ms), 516.2009.

Acetylation of 0.1 g of spicatin with 1 ml of acetic anhydride in 1 ml of pyridine for 12 hr at 0° followed by the usual work-up gave 0.095 g of a gum (**2c**) which was purified by preparative tlc (solvent petroleum ether–acetone–ether saturated with water, 4:1:1); ir bands at 1770, 720 (very strong), 1655 cm^{-1}; high-resolution mass spectrum *m/e* (composition, per cent) 558 (M^+, $C_{29}H_{34}O_{11}$, very weak), 438 ($C_{25}H_{26}O_7$, 2.5), 340 ($C_{20}H_{21}O_7$, 3.6), 259 ($C_{15}H_{15}O_4$, 5.1), 242 ($C_{15}H_{14}O_3$, 23.6), 141 ($C_7H_9O_3$, 41), and 81 (C_5H_5O, 100).

Fractions 81–112, total wt 13.8 g, contained mixtures; fractions 113 and 114, wt 11.5 g, although exhibiting a single spot on tlc, actually contained two substances which are still under investigation.

Extraction of *Liatris pycnostachya.* Above ground parts of *Liatris pycnostachya* (Michx.) Kuntze, wt 9.9 kg, colleced by Dr. N. C. Henderson in late August, 1972 in the vicinity of Belton, Mo., was extracted with $CHCl_3$ and worked up as usual. The crude gum, wt 80 g, was chromatographed over 1 kg of silicic acid, 600-ml fractions being collected. Fractions 1–40 (benzene) gave 30 g of crude spicatin. Fractions 41–50 (benzene–$CHCl_3$, 1:1) gave 5 g of a gum which was purified by preparative tlc, and was shown to be identical with synthetic **1c,** prepared from spicatin (*vide infra*), by ir and nmr spectroscopy and by mixed tlc. Further elution of the column with $CHCl_3$ and $CHCl_3$–MeOH (10:1) gave mixtures.

Conversion of Graminichlorin (3) to Graminiliatrin (1a). A solution of 0.1 g of **3** in a few milliliters of $CHCl_3$ was placed on a 50-g column of acid-washed alumina or silica gel. Elution with 5% methanol in $CHCl_3$ gave 0.080 g of **1a,** characterized by ir, nmr, and tlc comparison with authentic material.

Conversion of Deoxograminiliatrin (2a) to 1a. A solution of 0.1 g of **2a** in 5 ml of $CHCl_3$ was oxidized with 0.1 g of *m*-chloroperbenzoic acid at 0° for 2 hr with stirring. The mixture was diluted with chloroform, washed with sodium metabisulfite and water, dried, and evaporated. The residual gum exhibited two spots on tlc. It was separated by preparative tlc on silica gel (solvent benzene–ethyl acetate 2:1). The substance with R_f 0.6 (0.06 g) was identical with graminiliatrin (**1a**) in all respects. The substance with R_f 0.55 (0.030 g) could not be induced to crystallize and was characterized as **4a:** ir bands at 3450, 1770, 1740, 1725, 1655, 1250, 1030, 960, and 880 cm^{-1}.

Anal. Calcd for $C_{22}H_{26}O_9$: C, 60.82; H, 6.03; O, 33.14. Found: C, 60.61; H, 5.98; O, 33.40.

Epoxidation of Spicatin. Epoxidation of 0.1 g of **2b** at 0° for 5 days in the manner described in the previous paragraph furnished a gum which exhibited two spots on tlc. Preparative tlc on silica gel gave starting material and 0.036 g of noncrystalline **1c,** identical with material isolated from *L. pycnostachya:* $[\alpha]^{22}_{Hg}$ −80° (*c* 0.20, $CHCl_3$); uv strong end absorption (ϵ_{210} 14,900); ir bands at 3502, 1770, 1715, and 1650 cm^{-1}; high-resolution mass spectrum *m/e* (composition, per cent) 532 (M^+, $C_{27}H_{32}O_{11}$, 0.5), 514 ($C_{27}H_{30}O_{10}$, 1.8), 435 ($C_{22}H_{27}O_9$, 2.6), 417 ($C_{22}H_{25}O_8$, 3.5), 357 ($C_{20}H_{21}O_6$, 1.6), 337 ($C_{17}H_{21}O_7$, 0.9), 319 ($C_{17}H_{19}O_6$, 1.7), 259 ($C_{15}H_{15}O$, 14.6), 179 ($C_{10}H_{11}O_3$, 8.4), 141 ($C_7H_9O_3$, 18.6), 99 ($C_5H_7O_2$, 81.4), and 81 (C_5H_5O, 38.4).

Anal. Calcd for $C_{27}H_{32}O_{11}$: C, 60.89; H, 6.06; O, 33.05; mol wt, 532.1942. Found: C, 59.99; H, 6.22; O, 33.56; mol wt (ms), 532.1921.

Hydrolysis of Graminiliatrin to 5a. A solution of 0.3 g of **1a** in 15 ml of methanol containing 0.5 g of K_2CO_3 in 2 ml of water was stirred in a nitrogen atmosphere. After 30 min the mixture was diluted with water and extracted with ethyl acetate. The washed and dried extract was evaporated and the solid residue was recrystallized from ethyl acetate–methanol to provide 0.1 g of **5a:** mp 197°; $[\alpha]^{22}$D −110.3° (*c* 0.17, MeOH); ir bands at 3400, 1760, 1230, 1055, 1020, 1015, 950, 920, and 810 cm^{-1}; significant peaks in the low-resolution mass spectrum at *m/e* 326 (M^+), 311 (M − CH_3), and 295 (M − CH_2OH).

Anal. Calcd for $C_{16}H_{22}O_7$: C, 58.89; H, 6.79; O, 34.32. Found: C, 58.96; H, 6.75; O, 34.52.

Acetylation of 0.040 g of **5a** at room temperature for 24 hr gave a solid which was recrystallized from methanol: yield of **5b** 0.040 g; mp 99°, $[\alpha]^{22}D$ −112.5° (*c* 0.5, $CHCl_3$); ir bands at 1780, 1740 (strong), 1250, 1040, 1030, 950, and 820 cm^{-1}; low-resolution mass spectrum *m/e* 410 (M^+), 395 (M − CH_3), 379 (M − CH_2OH), 368 (M − C_2H_2O), 351 (M − $C_2H_3O_2$), 309 (M − C_2H_2O − $C_2H_3O_2$), 290 (M − $2CH_3CO_2H$).

Anal. Calcd for $C_{20}H_{26}O_9$: C, 58.53; H, 6.39; O, 35.08. Found: C, 58.33; H, 6.35; O, 35.24.

Correlation of Spicatin with 1a and 2a. Hydrolysis of 0.3 g of **2a** with K_2CO_3 in aqueous methanol as described in the previous section followed by preparative tlc on silica gel gave **6,** wt 0.1 g, as the major product which could not be induced to crystallize and had clearly visible pmr signals at 4.65 d br (4.5, H-2), 5.64 br (H-3), 4.60 dd (11, 8), 4.1 m (H-8), 3.65 m (H-13), 3.35 (OMe), 2.75 (AB, H-14), 1.92 br (H-15), but was not further characterized. Epoxidation with *m*-chloroperbenzoic acid gave a mixture of two isomers, the major isomer having the same R_f as **5a.** Isolation by preparative tlc followed by acetylation in the usual fashion afforded **5b,** identical with authentic material by melting point, mixture melting point, and spectral comparison (ir, pmr).

Hydrolysis of 0.4 g of spicatin with K_2CO_3 in aqueous methanol under identical conditions gave a mixture of four products. The material with the same R_f as **6** was isolated by preparative tlc on silica gel (solvent benzene–ethyl acetate, 1:5), yield 0.115 g, ir and nmr spectrum superimposable on that of **6** as prepared in the previous paragraph. Epoxidation again gave a mixture of two products; the major isomer (**5a**) was isolated by preparative tlc and converted to the diacetate **5b,** identical with material from **1a** and **2a** by melting point, mixture melting point, and spectral comparison (ir, pmr).

Oxidation of 5a. A solution of 0.1 g of **5a** in 50 ml of acetone (Anal-R grade) was oxidized at 0° by dropwise addition of 1 ml of Jones' reagent with vigorous stirring. After 0.5 hr excess reagent was destroyed with isopropyl alcohol and the reaction mixture was diluted with water and extracted with ethyl acetate. Evaporation of the washed and dried extract gave a gum which showed two spots on tlc. Separation by preparative tlc on silica gel (solvent benzene–ethyl acetate, 1:1) gave **7** (major product, R_f 0.7) and **9a** (minor product, R_f 0.5). Crystallization of **7** from ethyl acetate afforded colorless prisms: yield 0.04 g; mp 173–175°, $[\alpha]^{22}D$ +65.6° (*c* 0.80, $CHCl_3$); uv λ_{max} 235 nm (ε 10,500); ir bands at 3500, 1775 (γ-lactone), 1725 (very weak, cyclopentanone), 1670 (enone), 1080, 1030, 930, and 870 cm^{-1}; low-resolution mass spectrum *m/e* 322 (M^+), 304 (M − H_2O).

Anal. Calcd for $C_{16}H_{18}O_7$: C, 59.62; H, 5.63; O, 34.75. Found: C, 59.58; H, 5.58; O, 34.61.

Acetylation of 0.02 g of **7** in the usual manner gave **8** as a gum (0.02 g): $[\alpha]^{22}D$ +45.5° (*c* 0.66, $CHCl_3$); ir bands at 1780 (γ-lactone), 1750 (cyclopentanone), 1735 (acetate), 1670 (enone), 1240, 1030, 920, 860, and 835 cm^{-1}; high-resolution mass spectrum did not exhibit the molecular ion, but had significant peaks at *m/e* (composition, per cent) 322.1040 (M^+ − C_2H_2O, $C_{16}H_{18}O_7$, 100), calcd 322.1051; 304.0944 (M^+ − $C_2H_4O_2$, $C_{16}H_{16}O_6$, 46.8), calcd 304.0946.

Recrystallization of the minor oxidation product from methanol furnished 10 mg of **9a:** mp 173°; $[\alpha]D$ +8.7° (*c* 0.86, MeOH); λ_{max} 238 nm (ε 11,000); ir bands at 3400, 1760 (γ-lactone), 1665 (enone), 1220, 1060, 980, 930, and 850 cm^{-1}; significant peaks in the low-resolution mass spectrum *m/e* 324 (M^+), 306 (M − 18), 293 (M − CH_2OH), 278 (M − 18 − 28).

Anal. Calcd for $C_{16}H_{20}O_7$: C, 59.25; H, 6.22; O, 34.53. Found: C, 59.16; H, 6.26; O, 34.72.

Acetylation of 20 mg of **9a** gave the diacetate **9b** as a gum: yield 18 mg; $[\alpha]^{22}D$ −8.5° (*c* 0.1, $CHCl_3$); ir bands at 1775 (γ-lactone), 1750 (acetates), 1675 (enone), 1240, and 1030 cm^{-1}. The high-resolution mass spectrum had significant peaks at *m/e* (composition, per cent) 408 (M^+, $C_{20}H_{24}O_9$, 1.3), 366 (M − 42, $C_{18}H_{22}O_8$, 8.1), 348 (M − 60, $C_{18}H_{20}O_7$, 28.8), 324 (M − 2 × 42, $C_{16}H_{20}O_7$, 2), 306 (M − 42 − 60, $C_{16}H_{18}O_6$, 5.6).

Anal. Calcd for $C_{20}H_{24}O_9$: mol wt, 408.14.19. Found: mol wt (ms), 408.1394.

Oxidation of Graminiliatrin. Oxidation of 0.15 g of **1a** in 40 ml of acetone with 1 ml of Jones' reagent in the manner described for **5a** and purification of the crude product by preparative tlc on silica gel (solvent benzene–ethyl acetate 2:1) gave **10** as a gum: wt 0.11; ir bands at 3500, 1720, and 1620 (conjugated ester), 1240 and 1030 cm^{-1}. The low-resolution mass spectrum exhibited significant peaks at *m/e* 432 (M^+), 275 (M^+ − 157), 274 (M − 158), 256 (M − 158 − 18). Because **10** decomposed on standing, elementary analysis was not attempted.

Deoxygenations of Spicatin. (A) A mixture of 0.125 g of spicatin, 4 g of zinc–copper couple, and 40 ml of absolute ethanol was refluxed for 4 days, cooled, and filtered through Celite. Evaporation of the filtrate gave a gum which was separated into starting material (0.030 g) and deoxospicatin (**11,** 0.037 g) by preparative tlc on silica gel (solvent ether–$CHCl_3$–MeOH, 60:60:1). Substance **11** exhibited ir bands at 3510, 1770, and 1655 (conjugated γ-lactone), and 1715 cm^{-1} (strong conjugated esters). The high-resolution mass spectrum had significant peaks *m/e* (composition, per cent) 500 (M^+, $C_{27}H_{32}O_9$, 0.06), 440 ($C_{25}H_{28}O_7$, 3.4), 342 ($C_{20}H_{22}O_5$, 2.9), 326 ($C_{20}H_{22}O_4$, 8.4), 244 ($C_{15}H_{16}O_3$, 18.6), 228 ($C_{15}H_{16}O_2$, 42.4), 197 ($C_{10}H_{13}O_4$, 28.8), 141 ($C_7H_9O_3$, 25.4), 99 ($C_5H_7O_2$, 100), 81 (C_5H_5O, 72.8).

Anal. Calcd for $C_{27}H_{32}O_9$: C, 64.79; H, 6.44; O, 28.77. Found: C, 64.23; H, 6.46; O, 28.59.

Oxidation of 0.08 g of **11** with 0.1 g of *m*-chloroperbenzoic acid at 0° for 6 days and work-up of the reaction mixture as described previously gave a gum (0.05 g) which gave two spots on tlc. Preparative tlc on silica gel (solvent $CHCl_3$–ether–methanol, 15:15:1) afforded two noncrystalline products. The first, 18 mg, was identical (tlc, ir, nmr) with **1c.** The second, 12 mg, was assigned formula **12** rather than **4b** because of the H-14 frequencies (see Table I). The low-resolution mass spectrum exhibited significant peaks at 532 (M^+), 514 (M − H_2O), 435 (M − $C_5H_5O_2$), 417 (M − $C_5H_7O_3$), 357 (M − $C_7H_{11}O_5$), 277, 259, 141, and 99 (base peak).

Anal. Calcd for $C_{27}H_{32}O_{11}$: mol wt, 532. Found: 532.

(B) A mixture of 0.5 g of spicatin, 16 g of Zn–Cu couple, 100 ml of absolute ethanol, and 2 ml of HCl was refluxed for 5 days, cooled, filtered through Celite, and evaporated at reduced pressure. The residual gum showed three spots on tlc. Repeated preparative tlc on silica gel (solvent $CHCl_3$–ether–methanol, 30:30:1) permitted isolation of **13** as the middle fraction: wt 0.045 g; ir bands at 3480, 1775, 1710, and 1650 cm^{-1}. The high-resolution mass spectrum exhibited significant peaks *m/e* (composition, per cent) 346 (M^+, $C_{20}H_{26}O_5$, 0.2), 328 ($C_{20}H_{24}O_4$, 0.4), 263 ($C_{15}H_{19}O_4$, 1.7), 246 ($C_{15}H_{18}O_3$, 3.2), 228 ($C_{15}H_{16}O_2$, 4.9), 215 ($C_{15}H_{15}O_2$, 6.9), 83 (C_5H_2O, 100).

Anal. Calcd for $C_{20}H_{26}O_5$: mol wt, 346.1779. Found: mol wt (ms), 246.1806.

Registry No.—**1a,** 53142-34-0; **1b,** 53142-35-1; **1c,** 53177-31-4; **2a,** 53142-47-5; **2b,** 53142-46-4; **2c,** 53142-45-3; **3,** 53142-40-8; **4a,** 53177-32-5; **5a,** 53142-43-1; **5b,** 53142-44-2; **7,** 53142-41-9; **8,** 53142-42-0; **9a,** 53142-48-6; **9b,** 53142-49-7; **10,** 53142-36-2; **11,** 53142-37-3; **12,** 53142-38-4; **13,** 53142-39-5.

References and Notes

(1) (a) Part VI in a series "Constituents of *Liatris* Species." For Part V, see W. Herz and R. P. Sharma, *J. Org. Chem.,* **40,** 192 (1975). (b) This work was supported in part by U. S. Public Health Service Research Grant No. CA-13121 from the National Cancer Institute.

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(5) The flavone glycoside content of these collections and the analysis of the volatile constituents of our collection of *L. spicata* have been reported.[6,7]

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(8) Decoupling was carried out on **1a, 1b,** or **3** depending on which spectrum exhibited the best separation of signals.

(9) Evidence for the correctness of this assumption will be presented subsequently.

(10) Just as in the case of the tiglic acid–angelic acid isomer pair, the H-3′ signal of the *Z* isomer C would be expected to occur near 6.1 ppm, whereas the H-3′ signal of the *E* isomer would be expected at considerably lower field.

(11) Graminichlorin is an addition to the small number of know chlorine-containing guianolides.[12-14]

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(16) A small amount of an isomeric 3,4-epoxide which was not further characterized was also formed.
(17) S. M. Kupchan and M. Maruyama, *J. Org. Chem.*, **36**, 1187 (1971).
(18) Z. Samek, *Tetrahedron Lett.*, 671 (1970). Although some exceptions to the rule have been found,[4] it seems to be generally applicable to guaianolides.
(19) If the absolute configuration is as postulated, the observation that the CD curves of graminiliatrin and spicatin display negative Cotton effects near 260 nm could be interpreted as providing additional support for the trans fusion of the lactone ring.[20] However, the presence of one or two additional inherently symmetric but asymmetrically perturbed unsaturated ester chromophores in **1b** and **2b** could conceivably affect the CD curve so that the argument is not without pitfalls. A summary of X-ray results for several sesquiterpene lactones of established absolute configuration indicates that a C-6,C-7 trans lactone fusion gives rise to left-handed chirality (*i.e.*, the C=C—C=O torsion angle is negative).[21] Whether there is a direct connection between the chirality of the C=C—C=O grouping and the sign of the Cotton effect is still moot.[22]
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(24) For experimental details see previous papers of this series.
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(26) We wish to thank Dr. Thorleif Anthonsen, Institute for Organisk Kjem, Norges Tekniske Hogskole, Trondheim, for the authentic sample.

Total Synthesis of *dl*-9-Deoxyprostaglandin E_1

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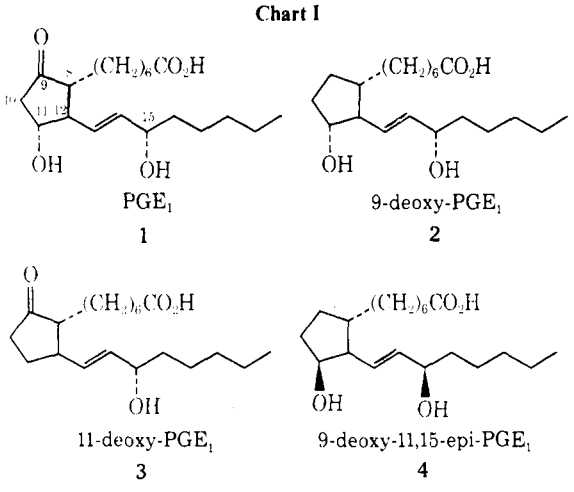
dl-9-Deoxyprostaglandin E_1 (PGE_1) **2** has been synthesized in nine steps from 2-carbomethoxy-3-oxo-1-cyclopenteneheptanoic acid methyl ester **36**. Details are provided of model studies and development of a synthetic procedure for preparation of one of the simplest PGE_1 model compounds **35** which contains all but one of the stereochemical features of PGE_1 **1**.

Extensive work has been carried out for several years with 11-deoxyprostaglandins **3**,[1,2] but only recently have accounts appeared of work with the 9-deoxyprostaglandins **2**.[3-5] These reports have prompted us to describe our synthesis of this type, which was disclosed previously in the patent literature[6] (Chart I).

Chart I



We also now describe the model experiments which were carried out to establish the stereochemical assignments in this synthetic sequence and that used for the synthesis of prostaglandin E_1 **1** itself.[7]

Reaction of a mixture of the carbinols **5** and **6**, obtained by $LiAlH_4$ reduction of a mixture of *cis*- and *trans*-2-carbomethoxycyclopentanols, with *p*-nitrobenzaldehyde dimethyl acetal[8] and acid catalysis yielded only one *p*-nitrobenzylidene cyclic acetal **15**. This was shown to be derived from the cis hydroxycarbinol **5** by cleavage back to this compound, which had been obtained also by $LiAlH_4$ reduction of the low-boiling *cis*-2-carbomethoxycyclopentanol. Separation of the *cis*- and *trans*-2-carbomethoxycyclopentanols could be achieved conveniently by fractional distillation using a spinning band column.[9] The cis assignment to the crystalline 2-hydroxymethylcyclopentanol **5** was rigorously proved by conversion into the oxetane **16** by Kovács *et al.*[10] (Chart II). This selective acetalization was used for assignment of stereochemistry to intermediates **44** and **46** in the 9-deoxyprostaglandin synthesis.

One important synthetic operation we had to accomplish for synthesis of either PGE_1 **1** or 9-deoxy-PGE_1 **2** was attachment of the *trans*-allylic alcohol side chain to the cyclopentane ring. The most attractive route seemed to be reaction of an appropriate cyclopentane aldehyde with a Wittig reagent and then metal hydride reduction of the resultant enone. The snag with this route was that the Wittig reagent could function as base as well as nucleophile and cause at least epimerization of the aldehyde, if not elimination. To explore the viability of this route for use in a prostaglandin synthesis, we therefore decided to attempt synthesis of cis and trans 2-methoxycyclopentane aldehyde **17** and **18**. The mixture of 2-carbomethoxy- and carboethoxycyclopentanols was O-methylated.[11,12] The cis and trans mixture of methoxy carbinols **9** and **10**, obtained by $LiAlH_4$ reduction of the mixture of O-methylated esters, was separated by fractional distillation through a spinning band column. The lower boiling fraction was assigned the cis configuration **9** by correlation with material obtained directly from the pure *cis*-2-carbomethoxycyclopentanol. A similar correlation was carried out for the high-boiling trans isomer **10**. The oxidation of the *trans*-2-hydroxymethyl-1-methoxycyclopentane **10** to the *trans*-2-methoxycyclopentane aldehyde **18** proceeded well with Jones reagent. Unfortunately, Jones reagent did not work for the preparation of the *cis*-2-methoxycyclopentane aldehyde **17** from the cis carbinol **9**. Instead a little used procedure due to Barton[13] was tried on the carbinols **9** and **10** and worked extremely well, providing both cis and trans 2-methoxycyclopentane aldehydes **17** and **18** free of each other. Not surprisingly, the trans aldehyde **18** was more stable and yielded normal