filtering, and evaporation, a white solid was obtained which was recrystallized from benzene–petroleum ether: 11 g; mp 121–122°; ir (KBr) 3040, 1580, 1485, 1435, 1360, 1220, 1110, 820 cm^{-1}; nmr ($DCCl_3$) 7.80–6.65 (m, 20 H), 4.70 ppm (s, 2 H).

Condensation and Subsequent Addition of HX. Pure benzyl 6-oxopenicillanate and 3 equiv of *N*-phenoxyacetyliminophosphorane were refluxed in benzene for 44 hr. To the cool mixture an excess amount of HX was added rapidly. The solvent was removed to give a brown syrup which was purified by chromatography.

Benzyl 6α-methoxy-6β-phenoxyacetamidopenicillanate: 42% yield; R_f 0.41 (1:20 Et_2O–CH_2Cl_2); ir (film) 3330, 1780, 1745, 1695, 1600, 1500, 1325, 1215 cm^{-1} nmr ($DCCl_3$) 7.62 (s, br, 1 H), 7.35–6.85 (m, 10 H), 5.62 (s, 1 H), 5.17 (s, 2 H), 4.52 (s, 2 H), 4.45 (s, 1 H), 3.48 (s, 3 H), 1.40 (s, 3 H), 1.36 ppm (s, 3 H); $[\alpha]^{25}D$ +213° (*c* 0.92, $CHCl_3$).

Anal. Calcd for $C_{24}H_{26}N_2SO_6$ (470.54): C, 61.26; H, 5.57; N, 5.95; S, 6.81. Found: C, 61.44; H, 5.70; N, 6.04; S, 6.77.

Benzyl 6α-cyano-6β-phenoxyacetamidopenicillanate: 36% yield; R_f 0.43 (1:30 Et_2O–CH_2Cl_2); ir (film) 3300, 1795, 1740, 1695, 1600, 1500, 1315, 1215 cm^{-1}; nmr ($DCCl_3$) 7.62 (s, 1 H), 7.40–6.85 (m, 10 H), 5.88 (s, 1 H), 5.21 (s, 2 H), 4.60 (s, 2 H), 4.52 (s, 1 H), 1.38 ppm (s, 6 H); $[\alpha]^{25}D$ +179° (*c* 0.94, $CHCl_3$).

Anal. Calcd for $C_{24}H_{23}N_3SO_5$ (461.51): C, 61.92; H, 4.98; N, 9.03; S, 6.89. Found: C, 61.79; H, 5.04; N, 8.89; S, 6.76.

Hydrogenolysis of Benzyl Esters. The benzyl ester was hydrogenated in ethyl acetate over 10% palladium on charcoal for 4 hr at room temperature and 1 atm pressure. The resulting mixture was filtered and the filtrate was extracted twice with cold 1*N* potassium bicarbonate solution. The combined aqueous extracts were washed once with ether and cooled to 0°. Ether was added and the stirred mixture was acidified to pH 2 by slow addition of 12*N* hydrochloric acid. The ether layer was separated and the aqueous layer extracted three times with ether. The organic phase was washed with distilled water, dried (Na_2SO_4), and evaporated to yield an oil. This oil, after freeze-drying from benzene, gave a white solid as the product.

6α-Methoxy-6β-phenoxyacetamidopenicillanic acid: 68% yield; ir ($CHCl_3$) 3380, 1780, 1725, 1695, 1600, 1495, 1205 cm^{-1}; nmr ($DCCl_3$) 8.20 (s, br, 1 H), 7.68 (s, 1 H), 7.36–6.86 (m, 5 H), 5.60 (s, 1 H), 4.58 (s, 2 H), 4.45 (s, 1 H), 3.53 (s, 3 H), 1.55 (s, 3 H), 1.50 ppm (s, 3 H).

6α-Cyano-6β-phenoxyacetamidopenicillanic acid: 58% yield; ir ($CHCl_3$) 3380, 1795, 1725, 1695, 1600, 1490, 1235 cm^{-1}; nmr ($DCCl_3$) 8.40 (s, br, 1 H), 7.60 (s, 1 H), 7.38–6.86 (m, 5 H), 5.88 (s, 1 H), 4.62 (s, 2 H), 4.52 (s, 1 H), 1.57 (s, 3 H), 1.42 ppm (s, 3 H).

Acknowledgment. This work was assisted financially by the Sloan Basic Research Fund.

Registry No. —1, 39126-59-5; **2**, 53198-76-8; **3a**, 35353-37-8; **3b**, 53198-77-9; **4a**, 35353-34-5; **4b**, 53198-78-0; **5**, 39486-17-4; *N*-phenoxyacetyliminotriphenylphosphorane, 53229-99-5, phenoxyacetyl chloride, 4461-31-8; sodium azide, 26628-22-8; triphenylphosphine, 603-35-0.

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Ligantrol and Ligantrol Monoacetate, Two New Linear Polyoxygenated Diterpenes from *Liatris elegans*[1]

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The geranylnerol derivative ligantrol (**1a**) and its monoacetate (**1b**) have been isolated from *Liatris elegans* (Walt.) Michx. and their structures established. The absolute stereochemistry assigned to C-11 and C-14 (11*R*, 14*S*) was deduced by degradation to a known lactone **16** of established absolute configuration.

As part of our study of the genus *Liatris* (tribe Eupatoriae, Compositae)[1a,2] which elaborates various cytotoxic and antitumor sesquiterpene lactones[3-5] we have examined *Liatris elegans* (Walt.) Michx.,[6] a species widely distributed in the Southern U.S. In the present communication we report isolation and structure determination of ligantrol (**1a**) and ligantrol monoacetate (**1b**), two highly oxygenated linear diterpenes, which are derivatives of geranylnerol. Future reports will deal with sesquiterpene lactones of this and other *Liatris* species.

Ligantrol, $C_{20}H_{36}O_5$, was obtained as a gum, $[\alpha]^{25}D$ +5.1°, and attempts to crystallize it were unsuccessful. It had ir bands at 3400, 1600, 1085, and 960 cm^{-1} and only end absorption in the uv. Ligantrol and the naturally occurring ligantrol monoacetate (**1b**), $[\alpha]^{25}D$ +25°, on acetylation with acetic anhydride–pyridine furnished the same triacetate (**1d**), $[\alpha]^{25}D$ −4.3°, which had ir bands at 3500, 1735, 1660, 1240, 1060, and 900 cm^{-1}. It was clear from these results that ligantrol had three acylable hydroxyl groups; as the ir spectrum of the triacetate still exhibited hydroxyl absorption, the other two oxygens had to be two tertiary hydroxyls or one tertiary hydroxyl and one ethereal oxygen. Since **1d** was not attacked by $CrO_3 \cdot 2Py$, the possibility of a hindered secondary hydroxyl group was ruled out.

The cmr spectrum of ligantrol (Figure 1) proved to be very helpful at this stage. The noise-decoupled spectrum accounted for all 20 carbon atoms and was also indicative of purity, as the decoupled spectrum of a mixture would have given rise to extra signals. The off-resonance decoupled spectrum displayed, in addition to ten difficult-to-disentangle signals, apparently all multiplets, in the range 23.3–32.3 ppm[9] downfield from TMS, two doublets (125.3 and 127.7) and two singlets (138.4 and 139.1 ppm)

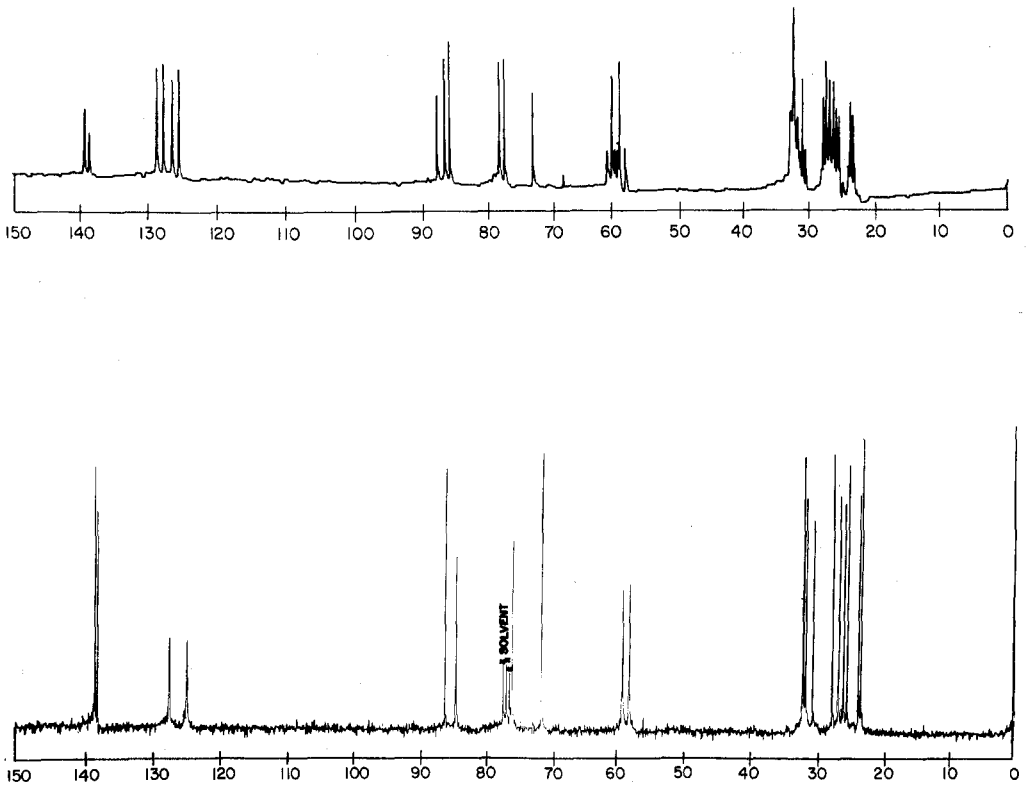
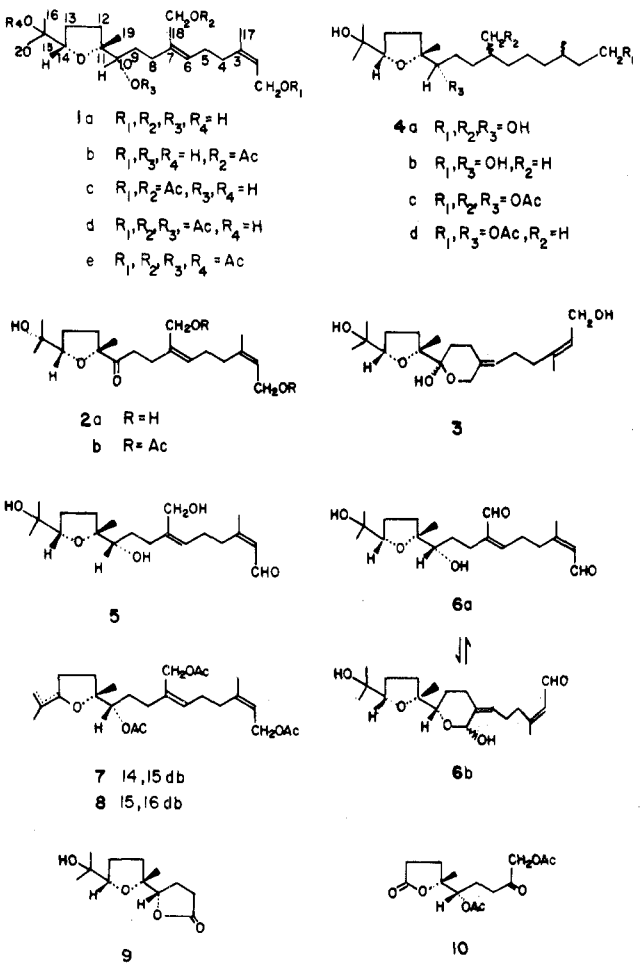
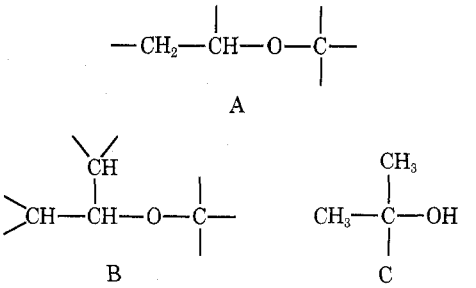


Figure 1. Top, off-resonance decoupled cmr spectrum of ligantrol. Bottom, noise-decoupled cmr spectrum of ligantrol.



which clearly indicated the presence of two trisubstituted double bonds. Six signals in the range 58.6–86.3 revealed that the five oxygen atoms of ligantrol are attached to six carbon atoms which is only possible if one of the oxygens is present as an ether function. The off-resonance spectrum further classified these carbons as two primary (triplets at 58.5 and 59.6), two secondary (doublets at 76.3 and 84.7), and two tertiary (singlets at 71.8 and 86.3 ppm).

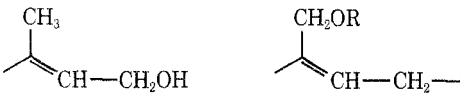
The pmr spectrum of ligantrol (Table I) indicated that the two trisubstituted and unconjugated (because of the lack of uv absorption) double bonds were of the type $>C{=}CHCH_2$ because of the presence of two slightly broadened vinyl triplets near 5.4 ppm. One of these carried a vinyl methyl group as evidenced by a narrowly split multiplet at 1.72 ppm. Comparison of the pmr spectra of **1a, 1b,** and **1d** (Table I) further demonstrated that the three acetylable hydroxyl groups were of the type $>CHCH_2OH$, $>CCH_2OH$, the latter acetylated in ligantrol monoacetate and both giving rise to the cmr triplets at 58.7 and 59.8 ppm, and >CHCH(OH)CH< or $>CCH(OH)CH_2$, this giving rise to the cmr doublet at 76.4 ppm.[10] The chemical shift of a sharp triplet near 3.8 ppm which was unaffected by acylation and oxidation suggested the presence of a cyclic or acyclic ether of type A or B rather than an oxirane.[12] Presumably, this function was also responsible for the cmr doublet at 84.8 and the singlet at 86.3.[10]



Lastly the observation of three methyl singlets gave rise to the suspicion that the tertiary hydroxyl group was included in partial structure C which would be responsible for the remaining carbon signal in the C–O region, the sin-

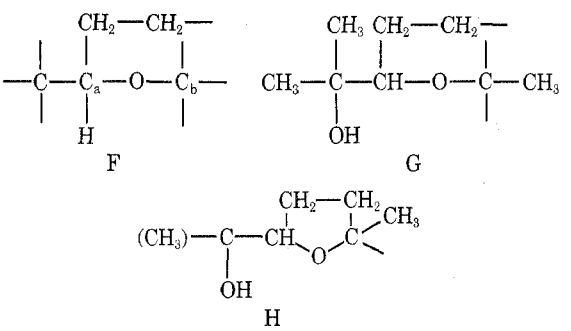
glet at 71.8 ppm.[10] Indeed, acetylation under stringent conditions (BF_3–Ac_2O) produced a tetraacetate **1e**[13] whose pmr spectrum (Table I) displayed two of the three methyl signals at considerably lower field consonant with this hypothesis; simultaneously, the ethereal proton had experienced a paramagnetic shift of 0.2 ppm, an observation which indicated its proximity to the tertiary hydroxyl group.

Decoupling experiments on ligantrol monoacetate **1b** revealed that the two primary alcohol functions were attached to the olefinic systems as in D and E. Thus, irradia-



D E,R = H or Ac

tion at the frequency of the superimposed vinyl protons collapsed the two-proton signal at 4.11 ppm (D) to an AB quartet and the two-proton signal at 4.60 ppm (E) to a singlet, while also effecting some changes in the region of the allylic methylenes. Conversely, irradiation at 4.11 ppm collapsed one of the vinyl triplets, the other remaining undisturbed, while irradiation at 3.53 (CHOH) only caused some changes in the methylene region. In addition, irradiation at the frequency of the ethereal proton (3.79 ppm) changed a two-proton multiplet at 1.88 to a triplet while irradiation in the reverse sense, *i.e.*, at 1.88 ppm, collapsed the triplet at 3.79 ppm to a singlet and affected the methylene region as well. Thus part structure A, not B, was correct and could be expanded to F where C_a most likely represented the point of attachment of partial structure C. If this were so, the remaining tertiary methyl group had to be located on C_b as in G.

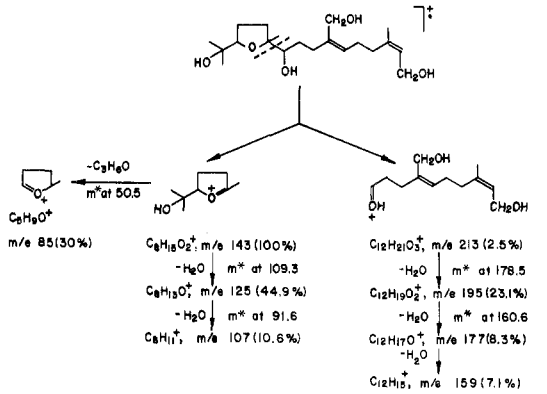


F G H

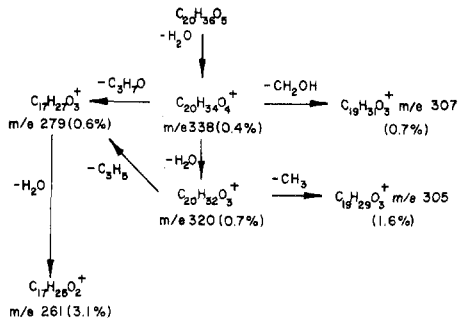
Formulas **1a** and **1b** (exclusive of stereochemistry) were biogenetically plausible structures for ligantrol and its monoacetate which incorporated the various partial structures and satisfied all other requirements. Their correctness was demonstrated unambiguously by the following transformations.

Catalytic hydrogenation of ligantrol furnished two products, **4a** by saturation of both double bonds and **4b**, a minor product, by concomitant hydrogenolysis of partial structure E. Comparison of the high-resolution mass spectra of **1a**, **4a**, and **4b** (see Schemes I–IV which are supported by metastable ions where indicated) revealed the following facts. While each substance gave rise to the same base peak at *m/e* 143 representing the ion $C_8H_{15}O_2$ which underwent loss of H_2O to $C_8H_{13}O$ or decomposition to C_5H_9O (*m/e* 85), another series of transitions in the mass spectrum of ligantrol, $C_{12}H_{21}O_3 \rightarrow C_{12}H_{19}O_2 \rightarrow C_{12}H_{17}O \rightarrow C_{12}H_{15}$, was shifted 4 mass units higher in the mass spectrum of **4a** and 12 mass units lower in the mass spectrum of **4b** and was much reduced in intensity. Thus, the most prominent re ult of electron impact on ligantrol appeared to be fragmentation into two "halves," one, the

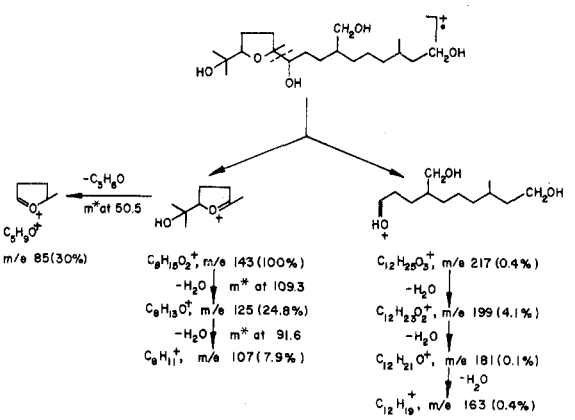
Scheme I
Mass Spectral Fragmentation of Ligantrol (A)



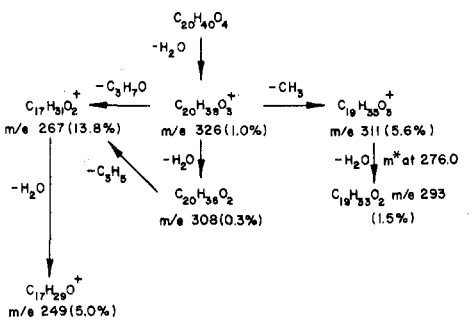
Scheme II
Mass Spectral Fragmentation of Ligantrol (B)



Scheme III
Mass Spectral Fragmentation of Tetrahydroligantrol



Scheme IV
Mass Spectral Fragmentation of 4b



$C_{12}H_{21}O_3$ portion, including partial structures D and E in some combination with C_4H_8O, the second, $C_8H_{15}O_2$, accounting for all the atoms of partial structure G. Ring closure of G to H provided an obvious rationalization of this

Table I
Pmr Spectra of Ligantrol and Derivatives[a]

Compd	H-1	H-2	H-6	H-10	H-14	H-17[b]	H-18	Me[b]	Ac[b]
1a	4.06[c]	5.38 t br (7)	5.38 t br (7)	3.56 dd (10, 3)	3.78 t (6.5)	1.72 m	4.11 br[d]	1.11, 1.14 1.25	
1b	4.11[c]	5.45 t br (7)	5.45 t br (7)	3.53 dd (10, 3)	3.79 t (6.5)	1.71 m	4.60 br[d]	1.13, 1.13 1.25	2.06
1c	4.54[c]	5.40 t br (7)	5.40 t br (7)	3.52 dd (10, 3)	3.80 t (6.5)	1.75 m	4.58 br[d]	1.13, 1.15 1.26	2.05 2.05
1d	4.52[c]	5.38 t br (7)	5.38 t br (7)	4.90 dd (10, 3)	3.74 t (6.5)	1.73 m	4.57 br[d]	1.09, 1.17 1.17	2.01, 2.03 2.05
1e	4.52[c]	5.36 t br (7)	5.36 t br (7)	4.90 dd (10, 3)	4.00 t (6.5)	1.73 m	4.56 br[d]	1.16, 1.40 1.44	1.96, 2.02 2.04
2b	4.51	5.38 t br (7)	5.38 t br (7)		3.88 t (6.5)	1.71 m	4.56 br[d]	1.08, 1.27 1.37	2.01 2.03
4c	4.10 t (6.5)[d]			4.89 dd (8, 2)	3.74 t (6.5)	0.90 d (6)	3.95 d (6)	1.12, 1.20 1.20	2.05, 2.05 2.07
4d	4.09 t (6.5)[d]			4.90 dd (8, 2)	3.74 t (6.5)	0.90 d (6)	0.85 d[b] (6)	1.12, 1.18 1.18	2.04 2.07
5	9.85 d (8)	5.88 d br (8)	5.27 t br (7)	3.47 dd (6.5)	3.74 t (1)	1.90[d]	4.05[c]	1.03, 1.06 1.19	
6a	9.88 d (8)	5.98 d br (8)	6.50 t br (7)	3.40 dd (10, 3)	3.77 t (6.5)	1.98 d (1.5)	10.06	1.08, 1.10 1.25	
6b	9.86 d (8)	5.80 d (8)	5.17 t br (7)	4.14 dd (10, 3)	3.79 t (6.5)	1.94 d (1.5)	5.77 br	1.08, 1.14 1.25	
7	4.52[c]	5.36 t br (7)	5.36 t br (7)	4.88 dd (10, 3)		1.73 m	4.56 br[d]	1.22 1.66 br, 1.66 br	2.02, 2.03 2.04
9				4.40 t (7)	3.80 t (6.5)			1.07, 1.10 1.10	
10				4.91 dd (10, 3)			4.58 br[d]	1.34	2.01, 2.08

[a] Run at 90 or 270 MHz in $CDCl_3$ solution using TMS as internal standard. Values are in parts per million. Multiplicities are indicated by the usual symbols: d, doublet; t, triplet; 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 three protons. [c] Intensity two protons. Center of AB part of ABX system. [d] Intensity two protons.

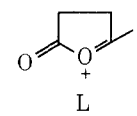
behavior in terms of the characteristic α fission of α-substituted tetrahydrofurans[14] depicted in Schemes I and III.

Selective acetylation of **1b** to **1c** (room temperature, 10 min), followed by oxidation with Collins reagent gave an unconjugated ketodiacetate **2b** which did not react with periodic acid. The oxidation also resulted in a significant downfield shift of one of the methyl signals (Table I), an observation which suggested that the new carbonyl group was attached to the one still available position of partial structure H. Hydrolysis of **2b** gave a substance whose ir and pmr spectrum (Table I) indicated its existence mainly in the hemiketal form **3** rather than in the ketodiol form **2a.** This facile formation of a hemiketal required interposition of four or five carbon atoms between the primary hydroxyl group of E and the secondary hydroxyl.

The same conclusion was reached by oxidation of ligantrol with activated MnO_2. This gave the terminal α,β-unsaturated aldehyde **5** and a second product whose pmr spectrum (Table I) showed that it was an equilibrium mixture of the bis-α,β-unsaturated dialdehyde **6a** and the aldehydic hemiacetal **6b,** as the result of interaction between the secondary hydroxyl group and the aldehyde formed by oxidation of partial structure E.

Ozonolysis of ligantrol followed by cleavage of the intermediate ketol with sodium metaperiodate resulted in formation of a γ-lactone $C_{12}H_{20}O_4$, $[\alpha]^{25}D$ +37.5°, whose pmr and high-resolution mass spectrum (α fission to *m/e* 143) retained all the features previously attributed to partial structure H. In addition, the lactone hydrogen now appeared as a sharp triplet at 4.40 ppm (Table I). The only structure compatible with these properties was **9,** a formula also fully consonant with the cmr spectrum.[15] The formation of **9** by loss of eight carbon atoms requires presence of the sequence C-1 through C-7 in the ligantrol formula and leads unequivocally to gross structure **1a.**

Confirmation for the substitution on the tetrahydrofuran ring of ligantrol was provided as follows. Dehydration of **1d** with thionyl chloride–pyridine gave a mixture of **7** and **8** (pmr spectrum). Ozonolysis of the mixture and chromatography permitted isolation and characterization of the diacetate **10** of a ten carbon γ-lactone whose pmr spectrum exhibited only one methyl resonance (singlet) and lacked the characteristic triplet of H-14. Moreover, the base peak in the high-resolution mass spectrum now corresponded to ion L (*m/e* 99, $C_5H_7O_2$) arising from α fission in **10.**



L

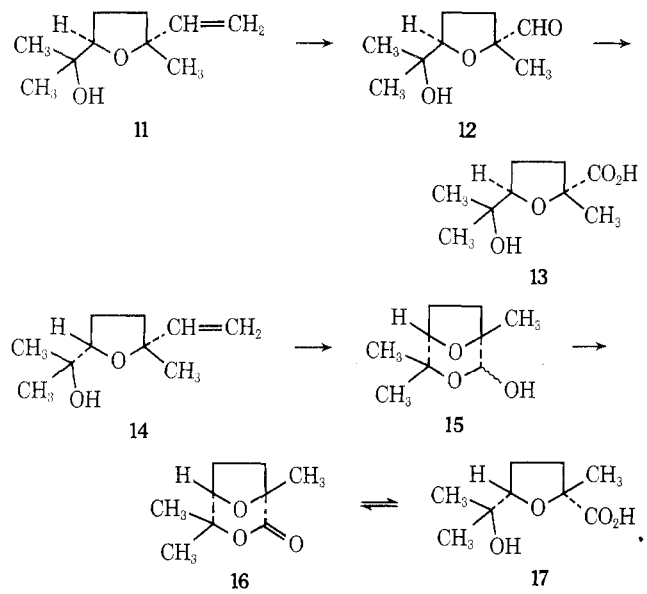
The stereochemistry attributed to ligantrol is based on the following observations. (1) The *Z* or nerol configuration around C-2–C-3 is evident because (a) the resonance of the methyl group on C-3 in **1a–e, 2b,** and **7** is in the range 1.71–1.75 ppm as in *cis,trans*-farnesol rather than near 1.64 ppm as in geraniol and *trans,trans*-farnesol;[16] (b) in the nmr spectra of the aldehydes **5, 6a,** and **6b,** the narrowly split vinylic methyl signal is found in the range 1.90–1.98 ppm, characteristic of the *Z* configuration, rather than at 2.15–2.18 ppm appropriate for the *E* configuration;[17] (c) in the cmr spectra of **1a** and **1b,** the absence of signals upfield from 23.3 ppm and from the region near 40 ppm indicates a

cis relationship of H-2 and the C-3 methyl group.[18]

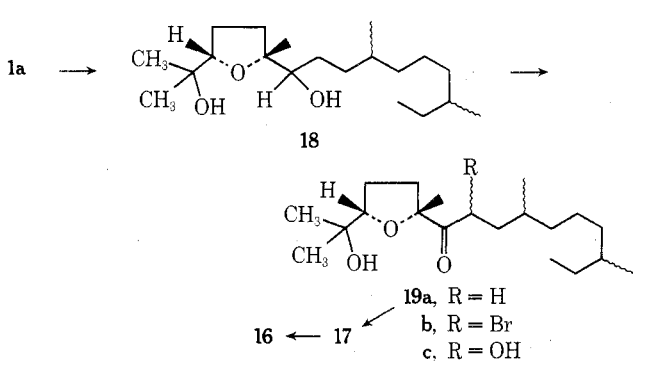
(2) The *Z* configuration around the C-6–C-7 double bond is evident from the pmr spectrum of **6a.** The chemical shift of the aldehyde proton on C-18 (10.06 ppm) is indicative of a trans relationship between the aldehyde function and the vinylic hydrogen, *cis*- aldehydes of this substitution pattern giving rise to signals in the range 9.26–9.4 ppm.[19]

(3) The absolute configuration of C-10 as *S* was established by applying Horeau's method[21] to **1c.** The optical yield of the recovered (*R*)-(−)-α-phenylbutyric acid was 8%.

(4) Kovàts and coworkers[22] differentiated between *cis*-(2*R*,5*S*)-and *trans*-(2*R*,5*R*)-2-methyl-2-vinyl-5-(α-hydroxyisopropyl)tetrahydrofuran as follows. Osmium tetroxide–periodate oxidation of the trans isomer **11** gave the aldehyde **12** and thence the acid **13,** whereas oxidation of the cis isomer **14** afforded a substance which was entirely in the hemiacetal form **15.** This could be oxidized to a lactone **16** which was interconvertible with an acid **17.** Since the hydroxyketodiacetate **2b** which is a homolog of either **12** or **14** exists entirely in the ketol, not the hemiketal, form, since the corresponding ketotriol is mainly in the hemiacetal form **3** and since treatment of **1d** or **4c** with BF_3–acetic anhydride results in acetylation rather than cyclic ether formation, we originally inferred that the two side chains on the tetrahydrofuran ring of ligantrol were trans (*i.e.* 11*R*,14*R* or 11*S*,14*S*) rather than cis.[23] However, eventual degradation of ligantrol to **16** demonstrated that it had the cis (11*R*,14*S*) absolute stereochemistry depicted in the formulas. This was accomplished as follows.

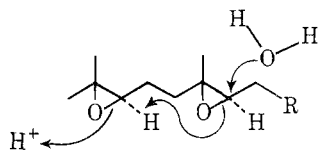


Catalytic hydrogenation of ligantrol (Pt, acetic acid) resulted in hydrogenolysis to **4b** and a mixture of isomers **18.**



Oxidation of **18** to **19a,** followed by bromination to **19b,** hydrolysis to **19c,** and subsequent cleavage with periodate gave a solid acid, presumably identical with **17.**[24] On heating, this was converted to a lactone whose physical properties and rotation corresponded to those reported[22] for **16.** Direct comparison established identity.

The functionalization of ligantrol at C-10, C-11, C-14, and C-15 is such that a biogenetic pathway involving at some stage the hydration of a 10,14-diepoxide or its biological analog appears plausible (see structure X below). If the diepoxide is derived from an all-trans or a cis,trans,trans precursor, as seems logical, *S* stereochemistry at C-10 and C-14 and *R* stereochemistry at C-11 of the eventual product coupled with mechanistic considerations (enzymatic trans hydration of a C-10,C-11 epoxide and inversion at C-14)[25,26] indicates that the hypothetical precursor diepoxide should possess the stereochemistry shown in structure X.[27]



Although tetrahydrofurans derived from farnesol are common, ligantrol appears to be the first diterpene of this genre. Moreover, the few linear diterpene alcohols so far known are derivatives of geranylgeraniol rather than geranylnerol.

Experimental Section[27]

Isolation of Ligantrol (1a) and Ligantrol Monoacetate (1b). *Liatris elegans* (Walt.) Michx., wt 21.9 kg, collected by Mr. R. L. Lazor on Sept 23, 1971 on the Sinkola plantation 4 miles west of the junction of U.S. 319 and State Road 755, Thomas Co., Georgia (Lazor no. 5586, voucher on deposit in herbarium of Florida State University), was extracted with chloroform and worked up in the usual manner.[28] The crude gum (80 g) was chromatographed over 1 kg of silicic acid (Mallinckrodt 100 mesh), 1-l. fractions being collected in the following order: 1–10 (benzene), 11–20 (benzene–$CHCl_3$, 5:1), 21–30 (benzene–$CHCl_3$, 1:1), 30–40 (benzene–$CHCl_3$, 1:5), 41–50 ($CHCl_3$), 51–60 ($CHCl_3$–MeOH, 20:1), 61–70 ($CHCl_3$–MeOH, 10:1), 71–80 ($CHCl_3$–MeOH, 5:1). All fractions were monitored by tlc. Fractions 12–18 yielded a crystalline sesquiterpene lactone whose constitution will be discussed elsewhere.

Fractions 52–59 on evaporation gave a gum which showed one major spot on tlc and was further purified by chromatography over silica gel. $CHCl_3$–MeOH (20:1) eluted 5 g of pure **1b:** $[\alpha]^{25}D$ +25° (*c* 1.2); ir bands at 3400 (OH), 1735, 1240 (acetate), 1660 (C=C), 1085, 1030 (C—O stretching), 960, 845 cm^{-1}. The low-resolution mass spectrum exhibited a weak molecular ion peak at *m/e* 398 and others at *m/e* 380 (M − H_2O), *m/e* 365, 362, and 338 (M − CH_3CO_2H). The high-resolution did not show the molecular ion but peaks at *m/e* (per cent, composition measured at high resolution) 365 (M − H_2O − CH_3) (0.3, $C_{21}H_{33}O_5$), 362 (M − H_2O − H_2O) (9.4, $C_{22}H_{34}O_4$), 338 (M − CH_3CO_2H) ($C_{20}H_{32}O_5$), 261 (2.4, $C_{17}H_{25}O_2$), 195 (0.3, $C_{12}H_{19}O_2$), 177 (1.8, $C_{12}H_{17}O$), 159 (4.6, $C_{12}H_{15}$), 143 (100, $C_8H_{15}O_2$), 125 (25.6, C_8H_3O), 107 (7, C_8H_{11}), 85 (17.4, C_5H_9O), 71 (18.9, C_4H_7O).

Anal. Calcd for $C_{22}H_{38}O_6$: C, 66.30; H, 9.61; O, 24.09. Found: C, 65.64; H, 9.69; O, 24.40.

Fractions 61–68 gave a gum which showed one major spot on tlc and was purified by chromatography over silica gel to give **1a** (10 g): homogeneous on tlc; $[\alpha]^{25}D$ +5.1° (*c* 0.6); ir bands at 3400 (hydroxyl), 1660 (double bond), 1085, 1020, 960, and 845 cm^{-1}. The elemental analysis was unsatisfactory. The high-resolution mass spectrum, whose main features are displayed in Schemes I and II, did not exhibit the molecular ion; the peak of highest mass number corresponded to $M^+ + 1$.

Anal. Calcd for $C_{20}H_{36}O_5$ (M + 1): mol wt, 357.2640. Found: mol wt (ms), 357.2642.

Acetylations of Ligantrol and Ligantrol Monoacetate. (A) Acetylation of 0.1 g of **1a** or 0.1 g of **1b** with 1 ml of acetic anhy-

dride and 0.5 ml of pyridine at room temperature for 24 hr followed by the usual work-up gave 0.1 g of **1d** as a gum: $[\alpha]^{25}D$ −4.3° (*c* 0.7); ir bands at 3500 (hydroxyl), 1735, 1240 (acetates), 1660 (C=C), 1060, 1030 (C—O stretching), 960, 900, and 850 cm^{-1}. The cmr spectrum exhibited signals due to 24 carbon atoms, 170.7 (two superimposed singlets, C=O) and 170.5 (singlet, C=O), 141.5 (C-7), 133.9 (C-3), 130.4 d (C-2), 120.0 d (C-6), 85.1 d (C-14), 84.1 (C-11), 77.2 d (C-10), 70.9 (C-15), 61.6 t and 60.9 t (C-1 and C-18), and 13 multiplets in the range 20.8–34.5 ppm downfield from TMS.

Anal. Calcd for $C_{26}H_{42}O_8$: C, 64.71; H, 8.77; O, 26.52. Found: C, 64.23; H, 8.63; O, 26.51.

When 0.1 g of **1d** was placed on a silica gel column (50 g) and eluted with methanol, hydrolysis to **1a** took place in quantitative yield.

(B) Exposure of **1a** or **1b** to acetic anhydride–pyridine at room temperature for 10 min followed by the usual work-up gave diacetate **1c** in 80% yield, together with triacetate **1d** (10%) and unreacted starting material (**1a** or **1b**, 10%). The diacetate **1c** was separated as an oil by preparative tlc on silica gel $PF_{254-355}$ (solvent benzene–ethyl acetate, 1:1). It had $[\alpha]^{25}D$ +9.0° (*c* 0.5); ir bands at 3420 (hydroxyl), 1725, 1240 (acetates), 1080, 1030 (C–O stretching), 955, 900, and 840 cm^{-1}.

Anal. Calcd for $C_{24}H_{40}O_7$: C, 65.43; H, 9.15; O, 25.47. Found: C, 65.25; H, 9.15; O, 25.52.

A solution of 0.360 g of α-phenylbutyric anhydride (1.16×10^{-3} mol) and 50 mg of **1c** (1.14×10^{-4} mol) in 2 ml was kept at room temperature for 48 hr. Excess anhydride was destroyed by addition of 5 ml of water. After 12 hr, the solution was extracted with ether which was washed with water and 5% $NaHCO_3$ solution. The combined aqueous layers were washed with chloroform, acidified with 1 *M* H_2SO_4, and extracted with chloroform. The washed and dried chloroform extracts were evaporated; the residue, wt 0.330 g, was pure α-phenylbutyric acid, $[\alpha]D$ −0.40°, which corresponded to an optical yield of 8%.

(C) A solution of 0.1 g of the triacetate **1d** in 3 ml of dry ether was cooled to 0°, mixed with 2 ml of freshly distilled acetic anhydride and 1.5 ml of freshly distilled BF_3–etherate, kept at 0° for 24 hr, poured into ice water, and extracted with $CHCl_3$. The washed and dried extract on evaporation gave a gum which showed two spots on tlc. It was separated by preparative tlc on silica gel $PF_{254-355}$ (solvent benzene–ethyl acetate, 2:1). The major component (0.07 g) was unreacted starting meterial **1d;** the minor component (0.01 g) was the tetraacetate **1e:** ir bands at 730, 1235 (very strong, acetates), 1030 (C–O stretching), 950, and 880 cm^{-1}; mass spectrum *m/e* 524 (M^+, $C_{28}H_{44}O_9$), 464 (M − CH_3CO_2H), 422 (M − CH_3CO_2H − C_2H_2O), 404 (M − $2CH_3CO_2H$), 344 (M − $3CH_3CO_2H$), 284 (M − $4CH_3CO_2H$), 185 (80%, $C_{10}H_{17}O_3$ usual base peak, but acetylated), 125 ($C_8H_{13}O$), 43 (base peak, C_2H_3O).

Oxidation of 1c. To a solution of 0.1 g of the diacetate **1c** in 15 ml of methylene chloride was added dropwise, with magnetic stirring, 50 mg of CrO_3–2Py complex, the reaction being followed by tlc. All starting material had disappeared after 6 hr. The reaction mixture was diluted with methylene chloride, washed, dried, and evaporated. The residual gum was purified by preparative tlc (solvent benzene–ethyl acetate, 2:1) to give 70 mg of **2b:** $[\alpha]^{25}D$ +8.6° (*c* 0.7); CD curve λ_{max} 285 nm ($[\theta]$ +1890); ir bands at 3420 (hydroxyl), 1735, 1725, 1260 (acetates), 1710 (ketone), 1030, 960, 920, 900, and 850 cm^{-1}. Low-resolution mass spectrometry revealed the molecular ion peak at *m/e* 438; other major peaks were at *m/e* 420 (M − H_2O), 410 (M − CO), 392 (M − H_2O − CO), 379 (M − $C_2H_3O_2$), 320 (M − H_2O − $C_2H_4O_2$), 303, 285, 259, 143 (base peak), 125, 107, and 85.

Anal. Calcd for $C_{24}H_{38}O_7$: C, 65.73; H, 8.73; O, 25.54. Found: C, 65.55; H, 8.67; O, 25.76.

The material was hydrolyzed by allowing 0.1 g of **2b** to stand in a 10% solution of KOH in ethanol for 2 hr. Acidification followed by the usual work-up gave 75 mg of **2a** whose ir and pmr spectra showed that it was predominantly in the hemiketal form **3:** ir bands at 3400, 1705 (very weak), 1050, 1030, 900, and 840 cm^{-1}; pmr signals at 4.09 (2 p, AB of ABX, H-1), 5.38 t br (2 p, H-2 and H-6), 3.88 t (6.5, H-14), 1.73 m (30, H-17), 4.25 br (2 p, H-18), 1.20, 1.17, 1.03 (three tertiary methyls); mass spectrum *m/e* 354 (M^+, $C_{20}H_{34}O_5$). Other major peaks were at *m/e* 336 (M − H_2O), 318 (M − $2H_2O$), 305 (M − H_2O − CH_2OH), 143 (usual base peak), 125, 107, and 85.

Hydrogenation of Ligantrol. A solution of 0.2 g of ligantrol in 15 ml of ethyl acetate was hydrogenated at atmospheric pressure in the presence of 50 mg of PtO_2. After 5 hr the catalyst was filtered and washed with ethyl actetate. Evaporation of the combined filtrate and washings gave a gum which showed two spots on tlc and was separated by preparative tlc on silica gel $PF_{254-355}$ (solvent $CHCl_3$–MeOH, 9:1). The major component (R_f slightly less than starting material) was **4a:** $[\alpha]^{25}D$ −12.2° (*c* 0.8); ir bands at 3350, 1085, and 1060 cm^{-1}. The high-resolution mass spectrum did not exhibit the molecular ion; significant peaks (in addition to those shown in Scheme III), which paralleled peaks shown in Scheme II for **1a,** were at *m/e* 342 (0.2, $C_{20}H_{38}O_4$), 327 (0.2, $C_{19}H_{35}O_4$), 283 (0.7, $C_{17}H_{31}O_3$), 265 (1.3, $C_17H_{29}O$). Acetylation of **4a** in the usual manner gave **4c,** ir bands at 3450, 1735, 1240, and 1035 cm^{-1}.

Anal. Calcd for $C_{26}H_{46}O_8$: C, 64.17; H, 9.53; O, 26.30. Found: C, 64.12; H, 9.51; O, 26.45.

The minor component (R_f 0.8) was characterized as **4b:** $[\alpha]^{25}D$ +10.2° (*c* 0.22); ir bands at 3350, 1080, and 1060 cm^{-1}. The high-resolution mass spectrum did not exhibit the molecular ion. Significant peaks (in addition to those in Scheme IV) which paralleled those in Schemes I and III were at *m/e* 201 (5, $C_{12}H_{25}O_2$), 183 (0.3, $C_{12}H_{23}O$), 165 (0.5, $C_{12}H_{21}$), 143 (100, $C_8H_{15}O_2$), 125 (36.2, $C_8H_{13}O$), 107 (6.4, C_8H_{11}). Acetylation of **4b** in the usual manner gave **4d:** $[\alpha]^{25}D$ −7.5° (*c* 0.6); ir bands at 3450, 1735, 1240, 1060, and 1030 cm^{-1}.

Anal. Calcd for $C_{24}H_{44}O_6$: C, 67.26; H, 10.35; O, 22.40. Found: C, 67.22; H, 10.30; O, 22.73.

MnO_2 Oxidation of Ligantrol. A solution of 0.1 g of **1a** in 15 ml of spectral grade chloroform was stirred with 0.2 g of active MnO_2, the reaction being monitored by tlc. After 24 hr, the mixture was filtered and the MnO_2 washed repeatedly with chloroform. The combined filtrate and washings were evaporated and the residue separated by preparative tlc on silica gel $PF_{254-355}$ (solvent benzene–ethyl acetate, 1:2). The more polar material, R_f 0.3, yield 53 mg, was characterized as the trihydroxy aldehyde **5:** $[\alpha]^{25}D$ −9.7° (*c* 1.0); ir bands at 3500 (hydroxyl), 1650 (conjugated aldehyde), 108, 1040, 960, 900, 845, and 800 cm^{-1}; uv λ_{max} 240 nm (ε 10,500); low-resolution mass spectrum *m/e* 354 (M^+, $C_{20}H_{34}O_5$). Other major peaks were at *m/e* 336 (M − H_2O), 321 (M − H_2O − CH_3), 305 (M − H_2O − CH_2OH), 143 (base peak, $C_8H_{15}O_2$), 125 ($C_8H_{13}O$), 107 (C_8H_{11}), and 85 (C_5H_9O).

The pmr spectrum of the less polar material, R_f 0.6, which was obtained only in small yield (15 mg) showed it to be an equilibrium mixture of **6a** and **6b** (Table I). Treatment of a purified sample of the trihydroxyaldehyde **5a** with active MnO_2 gave a quantitative yield of the equilibrium mixture after 1 hr:[30] ir bands at 3400, 1650, and 1080 cm^{-1}; pmr spectrum in Table I, low-resolution mass spectrum *m/e* 352 (M^+, $C_{20}H_{32}O_5$). Other significant peaks were at *m/e* 334 (M − H_2O), 321 (M − CH_2OH), 143 (base peak), 125, 107, and 85.

Ozonolysis of Ligantrol. A solution of 0.4 g of **1a** in 50 ml of chloroform (Anal-R grade) was ozonized at −30° for 15 min. The solvent was removed at 40° on a rotary evaporator. The residue was dissolved in 15 ml of MeOH, allowed to stand with 0.5 g of sodium metaperiodate in 2 ml of water overnight, diluted with water, and extracted with $CHCl_3$. The washed and dried extracts were evaporated and the residue purified by preparative tlc (solvent $CHCl_3$–MeOH, 19:1) to give 0.1 g of **9:** $[\alpha]^{25}D$ +37.5° (*c* 1.1); ir bands at 3500 (hydroxyl), 1750 (γ-lactone), and 1060 cm^{-1}. The low-resolution mass spectrum gave the correct molecular ion peak at *m/e* 228; other major peaks were at *m/e* 213 (M − CH_3), 195 (M − CH_3 − H_2O), 169 (M − CO_2), 152, 143, 125, and 107, the last three typical of the "left" side of the molecule.

Anal. Calcd for $C_{12}H_{20}O_4$: mol wt, 228.1361. Found: mol wt (ms), 228.1348.

Degradation of 1c to 10. A solution of 0.2 g of **1c** in 3 ml of dry pyridine was cooled to 0° and mixed with 0.2 ml of thionyl chloride with efficient stirring, the reaction being followed by tlc. After 30 min starting material had disappeared. The mixture was decomposed with ice water and extracted with chloroform. The washed and dried extracts were evaporated; the residual gum showed one major spot on tlc. However, preparative tlc (solvent benzene–ethyl acetate, 2:1) and pmr analysis showed that the major spot corresponded to a mixture of **7** and **8.** The low-resolution mass spectrum exhibited significant peaks at *m/e* 464 (M^+, $C_{26}H_{40}O_7$), 284 (M − $3CH_3CO_2H$), 125, and 43. The mixture (100 mg) was dissolved in 40 ml of Anal-R chloroform and ozonized at −30° for 15 min. After addition of 5 ml of dimethyl sulfide to decompose the ozonide, the mixture was stirred at room temperature overnight. Removal of solvent gave a residue which was separated by preparative tlc (solvent benzene–ethyl acetate, 1:1) to give 10 mg of **10** as a pure substance (pmr spectrum). The low-resolution mass spectrum exhibited the molecular ion at *m/e* 300; other major peaks were at *m/e* 258 (M − C_2H_2O), 240 (M − CH_3CO_2H), 227 (M −

$C_2H_2O - C_2H_3O$), 201 (M − 99), 185 (M − $2C_2H_2O - C_2H_3O$), 167 (M − $CH_3CO_2H - C_2H_2O - C_2H_3O$), 99 (base peak).

Anal. Calcd for $C_{14}H_{20}O_7$: mol wt, 300.1209. Found: mol wt (ms), 300.1204.

Degradation of 1a to 16. A solution of 0.3 g of **1a** in 20 ml of acetic acid was hydrogenated at atmospheric pressure in the presence of 0.25 g of PtO_2. After 4 hr, the catalyst was filtered and washed with ethyl acetate. Evaporation of solvent furnished a gum which showed two spots on tlc and was separated by preparative tlc on silica gel (benzene–ethyl acetate, 2:1) into **4b** (0.1 g) and **18** (0.15 g). The latter had pmr signals at 3.80 t (J = 6.5 Hz, H-14), 3.5 m (H-10), 1.25, 1.15, 1.13 (3 methyl singlets), and 0.85–0.95 ppm (two methyl doublets and one methyl triplet).

Oxidation of 0.15 g in 5 ml of CH_2Cl_2 with 0.2 g of $CrO_3 \cdot 2Py$ complex for 24 hr with stirring, dilution with 50 ml of $CHCl_3$, washing, drying, and evaporation at reduced pressure gave, after preparative tlc over silica gel (benzene–ethyl acetate, 3:1), 0.105 g of **19a** which had pmr signals at 3.90 t (J = 6.5 Hz, H-14), 1.40, 1.33, 1.14 (three methyl singlets), and 0.85–0.95 ppm (two methyl doublets and one triplet).

To a solution of 0.1 g of **19a** in 2 ml of acetic acid was added dropwise a solution of 50 mg of bromine in 0.2 ml of acetic acid containing a trace of HBr. The bromine color was discharged quickly; after 5 min the mixture was diluted with water and extracted with $CHCl_3$. The washed and dried extract was evaporated and the gummy residue (**19b**) was purified by preparative tlc on silica gel (benzene–acetate, 3:1): yield 0.105 g; pmr signals at 5.0 m (H-9), 3.91 t (J = 6.5 Hz, H-14), 1.50, 1.34, 1.16 (three methyl singlets), and 0.85–0.95 ppm (two methyl doublets and one triplet).

A solution of 0.095 g of the bromoketone **19b** in 5 ml of ethanol was stirred at room temperature in a nitrogen atmosphere with 0.5 ml of a 5% ethanol potassium hydroxide solution, the reaction being monitored by tlc. After 25 min, when all of the starting material had disappeared, the mixture was diluted with water and extracted with $CHCl_3$. The washed and dried extract was evaporated and the residue purified by preparative tlc over silica gel (benzene–ethyl acetate, 2:1) to give 0.065 g of **19c** which had pmr signals at 4.5 m (H-9), 3.90 t (J = 6.5 Hz, H-14), 1.40, 1.34, 1.16 (three methyl singlets), and 0.85–0.95 ppm (two methyl doublets and one triplet).

A solution of hydroxy ketone **19c** in 3 ml of methanol was oxidized with 0.25 g of $NaIO_4$ in 1 ml of water at room temperature for 5 hr, diluted with water, and extracted with $CHCl_3$. Evaporation of the solvent gave a gum which was separated by tlc on silica gel (MeOH–$CHCl_3$, 4:1). The most polar component which exhibited streaking on the plate (carboxylic acid) was a solid (**17**): yield 25 mg; mp 104–105° (lit. 96–97°,[22a] 108–109°[22b]); pmr spectrum (270 MHz) 5.2–5.7 (2 H, OH), 3.98 m (H-14), 1.7–2.6 (4 H), 1.53, 1.36, 1.15 ppm (three methyl singlets).

Acid **17** was kept at 150° for 15 min. On cooling, the solid deposited on the neck of the flask (mixture of **16** and **17**) was washed out with $CHCl_3$ and separated by preparative tlc. The less polar material was **16**: yield 5 mg; mp 80–81° (lit. 83–84°[22a,b]); $[\alpha]^{22}D$ +35° ($CHCl_3$, c 0.5) [lit. $[\alpha]D$ +40° ($CHCl_3$, c 1)];[22b] pmr signals (270 MHz) at 4.1 dbr (J = 7 Hz, H-14), 1.6–2.25 (four protons), 1.58, 1.55, and 1.33 ppm (three methyl singlets). Tlc behavior and pmr spectrum of authentic material[22b] were identical.

Registry No.—**1a,** 53198-13-3; **1b,** 53198-14-4; **1c,** 53198-15-5; **1d,** 53198-16-6; **1e,** 53198-17-7; **2a,** 53198-18-8; **2b,** 53198-19-9; **3,** 53198-20-2; **4a,** 53198-21-3; **4b,** 53198-22-4; **4c,** 53198-23-5; **4d,** 53198-24-6; **5,** 53198-25-7; **6a,** 53198-26-8; **6b,** 53198-27-9; **7,** 53198-28-0; **8,** 53198-29-1; **9,** 53198-30-4; **10,** 53198-31-5; **16,** 53274-44-5; **17,** 53198-32-6; **18,** 53198-33-7; **19a,** 53198-34-8; **19b,** 53198-35-9; **19c,** 53198-36-0.

References and Notes

(1) (a) Part V in the series "Constituents of *Liatris* Species." For Part IV, see H. Wagner, M. A. Iyengar, and W. Herz, *Phytochemistry,* **12,** 2063 (1973). (b) This work was supported in part by U. S. Public Health Service Research Grant No. CA-13121 from the National Cancer Institute.

(2) W. Herz and I. Wahlberg, *Phytochemistry,* **12,** 429 (1973).

(3) W. Herz and I. Wahlberg, *Phytochemistry,* **13,** 1421 (1973); *errata,* **14,** 315 (1974).

(4) W. Herz and I. Wahlberg, *J. Org. Chem.,* **38,** 2485 (1973).

(5) S. M. Kupchan, V. H. Davis, T. Fujita, M. R. Cox, and R. F. Bryan, *J. Amer. Chem. Soc.,* **93,** 4916 (1971).

(6) In our earlier report on flavone glycosides of *Liatris* species,[1a] this species was erroneously referred to as *L. elegans* (Walt.) Kuntze, due to confusion with an earlier name *Lacinaria elegans* (Walt.) Kuntze[7] with which it is synonymous. The analysis of the volatile constituents of our collection of *L. elegans* by glc–mass spectrometry has been reported elsewhere.[8]

(7) (a) J. K. Small, "Manual of the Southeastern Flora," University of North Carolina Press, Chapel Hill, N. C., 1933; (b) L. O. Gaiser, *Rhodora,* **48,** 165, 216, 273, 331 (1946).

(8) K. Karlsson, I. Wahlberg, and C. R. Enzell, *Acta Chem. Scand.,* **27,** 1613 (1973).

(9) In the noise-decoupled spectrum (bottom of Figure 1), the ten singlets in this range were clearly visible, although the two lowest field signals at 32.3 and 32.0 ppm were almost superimposed.

(10) Assignments are based on predicted cmr shifts,[11] comparison of the chemical shifts in the cmr spectra of **1a, 1b,** and **9,** and selective single frequency decoupling of C-10 and C-14.

(11) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemistry," Wiley-Interscience, New York, N. Y., 1972.

(12) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N. Y., 1969, p 199.

(13) The yield was only 15%, the remaining material being unchanged.

(14) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. II, Holden-Day, San Francisco, Calif., 1964, p 270.

(15) Aside from the signal of the carbonyl carbon at 176.6 ppm downfield from TMS, the low-field signals could be identified easily as arising from C-11 (singlet at 86.3), C-14 (doublet at 84.0), C-15 (singlet at 71.8)—all three essentially unchanged—and C-10 (doublet at 83.4, shifted downfield ~7 ppm from **1a**). The remaining seven signals were in the range 21.8–33.9 ppm.

(16) R. B. Bates and D. M. Gale *J. Amer. Chem. Soc.,* **82,** 5749 (1960); R. B. Bates, D. M. Gale, and B. J. Gruner, *J. Org. Chem.,* **28,** 1086 (1963). For more recent examples, see G. Stork, M. Gregson, and P. A. Grieco, *Tetrahedron Lett.,* 1391 (1969); J. Meinwald, W. R. Thompson, T. Eisner, and D. F. Owen, *ibid.,* 3485 (1971).

(17) L. M. Jackman and R. H. Wiley, *J. Chem. Soc.,* 2886 (1960); P. B. Venuto and A. R. Day, *J. Org. Chem.,* **29,** 2735 (1964); K. T. Suzuki, N. Suzuki, and S. Nozoe, *Chem. Commun.,* 527 (1971); J. Meinwald, K. Opheim, and T. Eisner, *Proc. Nat. Acad. Sci. U. S.* **69,** 1208 (1972).

(18) M. Jautelat, J. B. Grutzner, and J. D. Roberts, *Proc. Nat. Acad. Sci. U. S.,* **65,** 288 (1970); D. E. Dorman, M. Jautelat, and J. D. Roberts, *J. Org. Chem.,* **36,** 2757 (1971). In the cmr spectra of geraniol and *trans,trans*-farnesol, the C-3 methyl frequency is 16.2–16.3 and the C-4 frequency is 40.0–40.1 ppm downfield from TMS.

(19) R. E. Klinck and J. B. Stothers, *Can. J. Chem.,* **44,** 45 (1966); E. Bertele and P. Schuedel, *Helv. Chim. Acta,* **50,** 2445 (1967); K. C. Chan, R. A. Jewell, W. H. Nutting, and H. Rapoport, *J. Org. Chem.,* **33,** 3382 (1968); A. F. Thomas and M. Ozainne, *Chem. Commun.,* **47** (1969); U. Schwieter and S. Liaaen-Jensen, *Acta Chem. Scand.,* **23,** 1057 (1969). In rigid systems, the aldehydic proton appears at slightly lower fields (9.45–9.6 ppm).[20]

(20) C. S. Barnes and J. W. Lodger, *Aust. J. Chem.,* **15,** 322 (1962); C. J. W. Brooks and G. H. Draffan, *Tetrahedron,* **25,** 2887 (1969); T. Kato, T. Suzuki, M. Tanemura, A. S. Kumanireng, N. Otoani, and Y. Kitahara, *Tetrahedron Lett.,* 1961 (1971).

(21) A. Horeau, *Tetrahedron Lett.,* 506 (1961); 965 (1962); A. Horeau and H. B. Kagan, *Tetrahedron,* **20,** 2431 (1964); W. Herz and H. B. Kagan, *J. Org. Chem.,* **32,** 216 (1967).

(22) (a) D. Felix, A. Melera, J. Seibl, and E. sz. Kovàts, *Helv. Chim. Acta,* **46,** 1513 (1973); (b) F. Klein, H. Farnow, and W. Rojahn, *Justus Liebigs Ann. Chem.,* **675,** 73 (1964); E. Klein and W. Rojahn, *Tetrahedron,* **21,** 2353 (1965). We wish to thank Dr. Klein for an authentic sample of compound **16.**

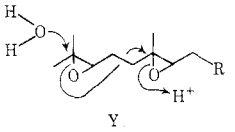
(23) Although in theory, this conclusion should have been verifiable by demonstrating the existence of NOE's between certain groups attached to the tetrahydrofuran ring, for example between H-16 and H-19, attempts to do so were frustrated by superposition or proximity of signals. No NOE was observed between H-10 and H-14, in accordance with expectations derived from inspection of models of cis and trans isomers.

(24) Due to the small scale on which the degradation was carried out, no attempt was made to purify **17,** especially since the literature values for the mp of **17** differ (see Experimental Section).

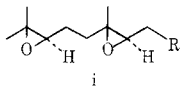
(25) D. M. Jerina, J. W. Daly, B. Witkop, P. Z. Nirenberg, and S. Udenfriend, *J. Amer. Chem. Soc.,* **90,** 6525 (1968); W. G. Niehaus, Jr., A. Kisic, A. Torkelson, D. J. Bedrarczyk, and G. J. Schroepfer, Jr., *J. Biol. Chem.,* **245,** 3802 (1970).

(26) Y. Suzuki, K. Imai, and S. Marumo, *J. Amer. Chem. Soc.,* **96,** 3703 (1974). The demonstration by these workers that fungal predominantly trans hydration of racemic 10,11-epoxyfarnesol is accompanied by a small amount of overall cis opening of the epoxide ring is not considered to invalidate this argument.

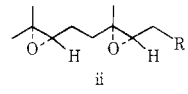
(27) The suggested scheme involves predominant nucleophilic attack on C-10 of the hypothetical precursor followed by intramolecular displacement at C-14 rather than initial nucleophilic attack on the tertiary center C-15 followed by displacement at C-11 (structure Y), in analogy with the observation of predominant nucleophilic attack on C-10 during the fungal hydration of 10,11-epoxyfarnesol.[26] Diepoxide i and diepoxide ii



Y

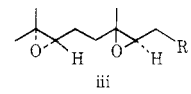


i

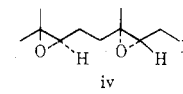


ii

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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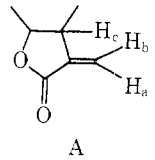
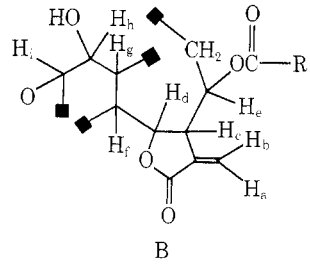
Five closely related guaianolides have been isolated from three *Liatris* species. *L. graminifolia* (Walt.) Kuntze gave graminiliatrin (**1a**), deoxygraminiliatrin (**2a**), and graminichlorin (**3**). *L. spicata* (L.) Kuntze yielded spicatin (**2b**) and *L. pycnostachya* (Michx.) Kuntze furnished 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



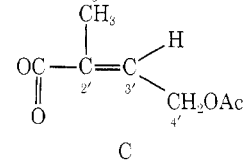
A



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