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Sesquiterpene Lactones of *Eupatorium recurvans*[1]

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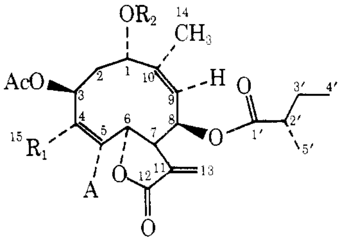
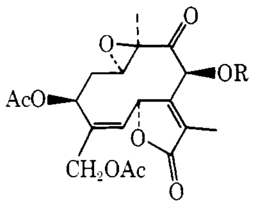
The isolation and structure determinations of three new heliangolides from *Eupatorium recurvans* Small are reported. The major lactone eurecurvin (**1a**) was a *cis*-$\Delta^{4,5}$,*cis*-$\Delta^{9,10}$-germacradienolide, as was a minor lactone constituent **1e.** The third lactone was a trans-$\Delta^{1(10)}$,cis-$\Delta^{4,5}$ isomer, **4a.** Details of the structure and stereochemistry were established by X-ray analysis of **1e** and **4a.**

In the present article we continue our reports[3-5] on constituents of *Eupatorium* species *sensu stricto* which have yielded various cytotoxic and antitumor sesquiterpene lactones and describe the isolation and structure determination of three new heliangolides **1a, 1e,** and **4a** from *Eupatorium recurvans* Small.[6] *E. capillifolium* (Lam.) Small, *E. compositifolium* Walt., *E. Leptophyllum* DC., and *E. pinnatifidum* Ell. yielded no significant sesquiterpene lactone fractions.[7]



1a, R_1 = CH_2OH; R_2 = H
b, R_1 = CH_2OAc; R_2 = H
c, R_1 = CH_2OAc; R_2 = Ac
d, R_1 = CHO; R_2 = H
e, R_1 = CH_3; R_2 = H
f, R_1 = CH_3; R_2 = H



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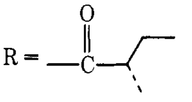

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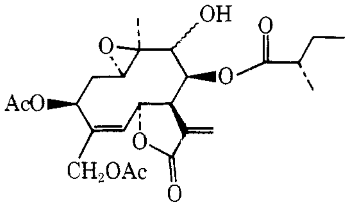

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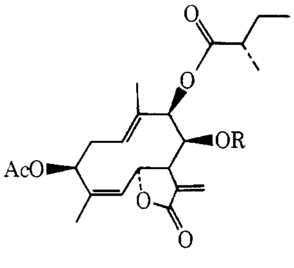
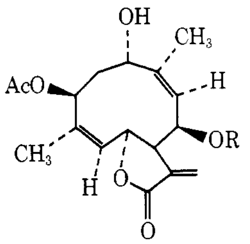
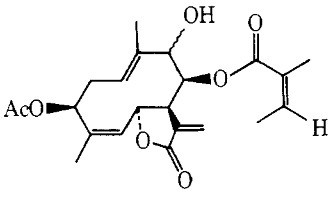


4a, R = H
b, R = Ac





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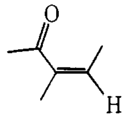
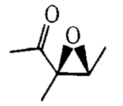
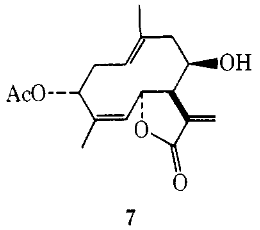
5a, R =



b, R =





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The major lactone component of *E. recurvans,* which we have named eurecurvin, $C_{22}H_{30}O_8$, mp 185–186 °C, was an α-methylene γ-lactone as evidenced by the usual criteria [^{1}H NMR spectral data in Table I, narrowly split doublets at 6.45 and 5.72 ppm (H_a and H_b), and appropriate signals of the ^{13}C NMR spectrum in Table II, particularly the triplet at 122.9 ppm]. That it was incorporated in partial structure A was shown by spin decoupling experiments on the lactone and its derivatives in various solvents, which will not be discussed in detail. A vinyl methyl group (broadened signal at 1.88 ppm) was found to be allylically coupled to H_f resonating at 5.44 ppm. Mass and NMR spectral analyses revealed the presence of two ester groups, an acetate and a 2-methylbutyrate.

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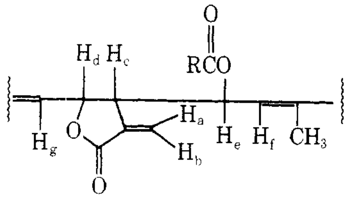
Table I. ^{1}H NMR Spectra of *E. recurvans* Constituents and Derivatives[a]

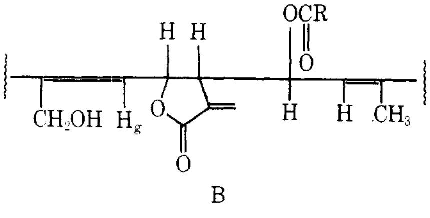
Compd	H-1	H-2	H-3	H-5	H-6	H-7	H-8	H-9	H-13	H-14[b]	H-15	Side chain & misc.
1a[c]	5.80 dbr (11, 2)	2.45 m (15, 11, 3) 2.64 m (15, 2, 4.5)	5.80 dbr (4.5, 3)	6.03 dbr (11)	6.43 dd (11, 9)	3.32 m (9, 2, 3, 3)	6.29 dbr (6, 2)	5.44 dbr (6)	5.72 d (3) 6.45 d (3)	1.90 br	4.47 br[d]	2.46 m (H-2′), 1.43, 1.72 m (H-3′),0.81 t (H-4),[b] 1.23 (d (H-5′),[b] 2.16 (Ac)[b]
1a[e]	5.40 m	1.97 m 2.29 m	5.34 br	5.60 m	6.00 dd	3.14 m	5.40 m	5.40 m	5.60 d 6.30 d	1.70 br	4.09 t 4.24 t	2.43 m, 1.68, 1.48 m, 1.21 d,[b] 0.89 t,[b] 2.1 (Ac)[b]
1b[c]	5.67 dbr (11, 2)	2.43 m (15, 11, 3) 2.55 m (15, 2, 4.5)	5.79 dbr (4.5, 3)	5.88 br (11)	6.43 dd (11, 9)	3.32 m (9, 2, 3, 3)	6.34 dbr (2, 6)	5.47 dbr (6)	5.74 d (3) 6.47 d (3)	1.90 br	4.69 d (15) 4.90 d (15)	Side chain as in **1a**: 2.06, 2.14 (Ac)[b]
1c[c]	6.71 dbr (11, 2)	2.28 m (15, 11, 3) 2.40 m (15, 2, 4.5)	5.74 dbr (4.5, 3)	5.91 dbr (11)	6.44 dd (11, 9)	3.30 m (9, 2, 3, 3)	6.32 dbr (2, 6)	5.53 dbr (6)	5.74 d (3) 6.48 d (3)	1.82 br	4.67 dbr (15) 4.83 dbr (15)	Side chain as in **1a**: 1.96, 2.06 (Ac)[b]
1d[c]	5.80 dbr (11, 2)	2.48 m	5.74 dbr (4.5, 3)	6.75 dbr (11)	6.45 dd (11, 9)	3.53 m	6.35 dbr (2, 6)	5.41 dbr (6)	5.80 d (3) 6.50 d (3)	1.66 br	9.64	Side chain as in **1a**: 2.13 (Ac)[b]
1e[f]	5.28 dbr[g] (10.5, 3)	2.20 m (16.5, 10.5) 3 2.01 m (16.5, 3, 3)	5.36 ddbr (6, 3)	5.28 dbr[g] (11)	5.96 dd (11, 9)	2.83 m (9, 1.5, 3, 3)	5.89 dbr (6, 1.5)	5.36 d (6)	5.58 d (3) 6.34 d (3)	1.83 br	1.72 br[b]	2.44 m (H-2′), 1.49 m, 1.67 m (H-3′), 0.92 t (H-4′),[b] 1.19 d (H-5′),[b] 2.14 (Ac)[b]
1e[e]	5.34 m	1.92 m 2.27 m	5.25 dd	5.34 m	5.97 dd	3.05 m	5.34 m	5.34 m	5.55 d 6.14 d	1.69 br	1.80 br	Side chain as in **1a**: 2.1 (Ac)[b]
2a[f]	3.85 dd 11, 3)	1.59 m 2.63 m	5.46 dd (6, 2)	5.20 dbr (11)	6.33 dq (11, 1.7)		5.10		1.94 d[b] (1.7)	1.26	4.50 dbr (15) 4.60 dbr (15)	Side chain as in **1a**: 2.07, 2.18 (Ac)[b]
2b[f]	3.92 dd (11, 3)	1.75 m 2.62 m	5.43 dd (6, 2)	5.18 dbr (11)	6.36 dq (11, 1.7)		4.42		2.01 d[b] (1.7)	1.26	4.50 dbr (15) 4.63 dbr (15)	2.07, 2.19 (Ac)[b]
3[f,h]	3.93 m	1.67 m 2.58 m	5.33 m	5.61 dbr (10)	5.69 m	3.07 m	5.69 m	5.33 m	5.90 d (3) 6.43 d (3)	1.32	4.64 br	Side chain same as in **1a**: 2.03, 2.11 (Ac)[b]
4a[f]	5.33 ddbr (10, 4)	2.28 m (16, 6, 4) 2.73 m (16, 10, 3)	5.26 ddbr (6, 3)	5.19 dbr (11, 1.5)	5.82 dd (11, 2)	2.84 m	4.12 br (~4, 2)	5.22 br (~4)	5.73 d (2) 6.40 d (2)	1.85 br	1.79 d (1.5)	Side chain as in **1e**: 2.03 (Ac)[b]
4b[f]	5.36 m (10, 4)	2.33 m (16, 6, 4) 2.74 (16, 10, 3)	5.28 dd (6, 3)	5.18 dbr (11, 1.5)	5.79 dd (11, 2)	2.98 m	5.54 br (~4, 2)	5.36 br (~4)	5.85 d (2) 6.40 d (2)	1.84 br	1.81 d (1.5)	Side chain as in **1e**: 2.03, 2.11 (Ac)[b]

[a] Run at 270 MHz on a Bruker HX-270 instrument with Me_4Si as an internal standard. Values are in ppm: d, doublet; br, broadened singlet; m, multiplet; t, triplet. Unmarked signals are singlets. Values in parentheses are coupling constants in hertz. [b] Intensity of three protons. [c] C_5D_5N solution. [d] Intensity of two protons. [e] $(CD_3)_2CO$ solution. [f] $CDCl_3$ solution. [g] *J* values obtained by decoupling in C_5D_5N where signals are separated. [h] Run at 90 MHz.

Acetylation (acetic anhydride–pyridine) afforded a mono- and a diacetate, thereby establishing the presence of two hydroxyl groups. One of these was primary, as indicated by the downfield shift and conversion, on acetylation, of a two-proton signal at 4.47 ppm to two doublets (AB system) at 4.69 and 4.90 ppm in the monoacetate and at 4.67 and 4.83 ppm in the diacetate, and allylic, as indicated by MnO_2 oxidation of the parent compound to an α,β-unsaturated aldehyde (downfield shift of H_g from 6.03 to 6.75 ppm). The chemical shift of the aldehyde proton (9.64 ppm) was characteristic of a cis relationship between H_g and the aldehyde group, a conclusion which was confirmed by demonstration of an NOE between H_g and $-CH_2OH$ in the parent compound (15% signal enhancement). Consequently, A could be expanded to B.[8] The other hydroxyl group was secondary, as indicated by the downfield shift of a one-proton signal from 5.80 and 5.67 ppm in the parent compound and monoacetate **1b** to 6.71 ppm in the diacetate **1c**. Spin decoupling experiments with **1a**, **1b**, and **1c** also established the presence of unit C.



A



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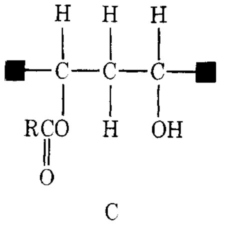


C

Differentiation between the two structural possibilities afforded by the combination of B and C and location of the isobutyrate ester function on C-8 was made possible by oxidation of monoacetate **1b** with Jones reagent. Three major products were isolated which, on the basis of their spectral properties, could be assigned structures **2a**, **2b**, and **3**, generated as the result of an allylic transposition involving the secondary hydroxyl group and the double bond to which H_g is attached. Consequently, the free hydroxyl group of eurecurvin monoacetate is on C-1 and not on C-3.[9] An analogous allylic trans position (without migration of the[11,13] double bond) had previously[12] served to correlate the antileukemic sesquiterpene lactone eupacunin (**5a**) with eupatocunin (**6**).

The fortuitous loss of the isobutyrate residue during the formation of **2b** clearly showed that it was attached to C-8 in the precursors **1b** and **1a** and that the acetate was located at C-3. That the 9,10 double bond was cis was demonstrated by

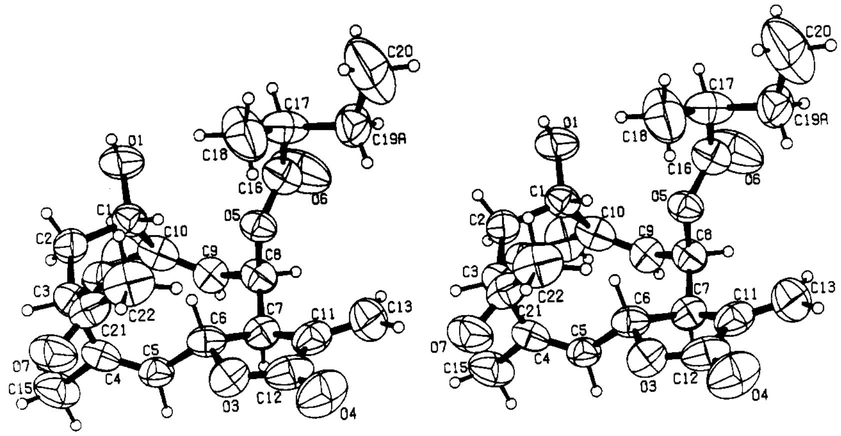


Figure 1. A stereoscopic drawing of a molecule of **1e**. The principal conformation of the isovalerate is shown.

Table II. ^{13}C NMR Spectra of *E. recurvans* Constituents[a]

Carbon atom[b]	**1a**[c]	**1f**[d]	**4a**[d]
1	65.8 d	65.1 d	124.7 d
2	35.4 t	32.4 t	28.7 t
3	72.4 d[e]	73.1 d[e]	74.2 d[e]
4	141.5	143.9	138.5
5	125.9 d	126.0 d	126.9 d
6	75.8 d[e]	74.1 d[e]	76.4 d[e]
7	49.8 d	47.5 d	47.8 d
8	69.1 d	67.0 d	80.9 d[e]
9	124.0 d	123.2 d	78.8 d[e]
10	142.5	139.0	136.2[f]
11	136.3	134.4	135.6[f]
12	170.9	169.2	169.7
13	122.9 t	121.9 t	123.6 t
14	19.9 q	17.6 q	14.2 q
15	65.3 t	23.3 q	23.1 q
1′	175.9	174.8	175.5
2′	42.7 d	41.5 d	41.1 d
3′	27.4 t	26.3 t	26.8 t
4′	10.8 q	11.6 q	11.6 q
5′	17.7 q	16.4 q	16.5 q
1″	170.9	169.2	170.2
2″	21.7 q	21.0 q	21.2 q

[a] Run at 67.9 MHz on a Bruker HX-270 instrument. Values are in ppm. Unmarked signals are singlets. [b] Assignments tentative and not verified by single frequency off-resonance decoupling. [c] CD_3OD solution. [d] $CDCl_3$ solution. [e,f] Assignments may be interchanged.

irradiation at the frequency of the C-10 methyl signal, which resulted in 17% enhancement of the H-9 signal. Analysis of the coupling constants $J_{7,13a}$, $J_{7,13b}$, $J_{6,7}$ and $J_{7,8}$ then showed that the lactone ring of eurecurvin must be trans fused and the C-8 ester side chain β.[13]

We defer discussion of the stereochemistry at C-1 until we have considered a second lactone (**1e**; $C_{22}H_{30}O_7$, mp 113–114 °C), which was isolated in small amount only and seemed to differ from eurecurvin primarily in lacking the primary hydroxyl group (see Tables I and II). Formation of a monoacetyl derivative **1f** from this lactone was accompanied by a downfield shift of a signal in the cluster near 5.3–6.36 ppm, thus identifying the resonance of H-1. Analysis of the ^1H NMR spectra of **1e** and **1f** was facilitated by performing the spin decoupling experiments in $CDCl_3$, C_6D_6, or C_5D_5N to separate relevant signals. This will not be discussed in detail. NOE studies showed that the two double bonds were cis (17% signal enhancement of H-5 on irradiation of H-15, 16% enhancement of H-9 on irradiation of H-14); moreover, the coupling constants indicated that the relative stereochemistry at C-1, C-3, C-6, and C-8 was the same as that of eurecurvin. However, there was no direct evidence for orienting the lactone ring toward C-6 and for attaching the acetate group to C-3 and the isobutyrate to C-8, instead of the reverse. To settle these points and to establish the stereochemistry at C-1,[14] an X-ray analysis of the minor lactone was undertaken.

Table III. Crystal Data for 1e and 4a

	1e	**4a**
Formula	$C_{20}H_{30}O_7$ (406.48)	$C_{20}H_{30}O_7$ (406.48)
System	Orthorhombic	Trigonal
Space group	$P2_12_12_1$	$P3_1$ or $P3_2$
a	9.812 (7) Å	10.548 (3) Å
b	14.375 (8) Å	
c	15.691 (7) Å	17.418 (5) Å
d_{calcd}	1.219 g cm^{-3}	1.206 g cm^{-3}
Z	4	3

Table IV. Lactone Ring Torsion Angles of 1e and 4a

C(6)-O(3)-C(12)-C(11)	ω_1	−7.8°	6.9°
C(13)-C(11)-C(12)-O(4)	ω_2	−9.9°	4.7°
C(11)-C(7)-C(6)-O(3)	ω_3	−24.6°	13.1°
C(5)-C(6)-C(7)-C(8)	ω_4	89.3°	136.1°

Crystal data for **1e** are listed in Table III. Figure 1 is a stereoscopic drawing of the molecule which represents the absolute configuration of the molecule (vide infra). The acetate and methyl isobutyrate functions are attached to C-3 and C-8, respectively, as in **1a**, and the configuration of the C-1 hydroxyl is α. The C-4,C-5 and C-9,C-10 bonds are essentially parallel, with the methyl carbons projecting below the plane of the ring. Tables V, VI, and VII, containing bond lengths, bond angles, and torsion angles, and Tables XI and XII, listing final atomic and final anisotropic thermal parameters, are available as supplementary material.

The lactone torsion angles listed in Table IV show that if **1e** possesses the absolute configuration shown in Figure 1, the chirality of the C=CC=O group is negative ($\omega_2 = -9.9°$) and, as usual,[15] paired with the sign of the C(α)–C(β)–C(γ)–O torsion angle (ω_3). The chirality of this chromophore has been related[16] to the Cotton effect of an α,β-unsaturated lactone; since both **1a** and **1e** exhibit negative Cotton effects, the absolute configuration is as shown in the formulas and is the same as in all other sesquiterpene lactones of authenticated stereochemistry.

The close correspondence in the NMR spectra of eurecurvin and lactone **1e**, which if examined in the same solvent differed significantly only in the shifts of protons and carbons in the vininity of the "extra" primary hydroxyl group of **1a** (see Tables I and II), indicated that the configuration of **1b** at C-1

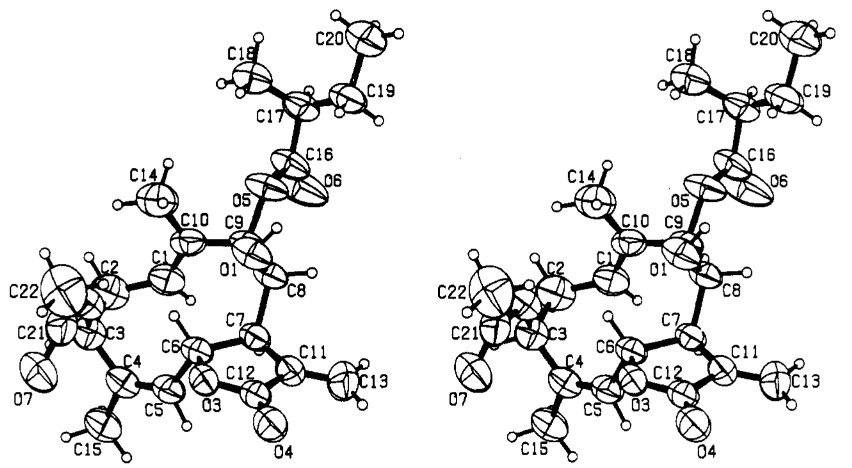


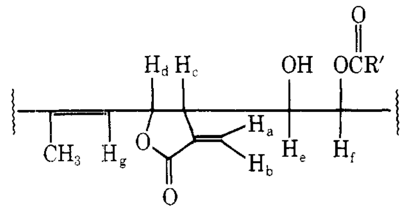
Figure 2. A stereoscopic drawing of a molecule of **4a** showing its conformation in the crystalline state.

was the same as that of **1e.** This was confirmed by application of Horeau's method to **1b,** which was esterified with excess (+)-α-phenylbutyric anhydride. The recovered α-phenylbutyric acid was negative (9.2% optical yield). Hence, the absolute configuration of eurecurvin at C-1 is *S* (OH α).

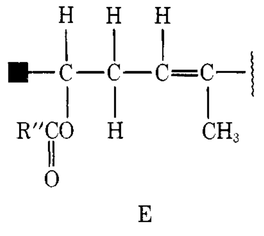
Thus, the conformations and stereochemistries of **1a** and **1e** are the same as those of eupacunin (**5a**) and eupacunoxin (**5b**).[17] It may be assumed that formulas **5a** and **5b** also represent the absolute configurations of these compounds although CD curves of **5a** and **5b** were unfortunately not available.[18]

The epoxides **2a/2b** and **3** must be trans epoxides because Jones oxidation of eupatocunin (**6**) with a trans 1,10 double bond afforded the same substance as the oxidation of eupacunin (**5b**). The stereochemistry at C-1 and C-2 shown in the formulas follows since other work emanating from this laboratory has shown[11] that the oxidative transposition of allylic alcohols, exemplified by conversion of **1a** and **5b** to compounds of this type, is accompanied by retention.

A third lactone, mp 129–131 °C, isomeric with **1e,** was isolated in a small amount only. It incorporated the usual α,β-unsaturated lactone function: two vinyl methyls (broadened singlet and narrowly split doublet at 1.85 and 1.79 ppm), a secondary hydroxyl group (signal at 4.12 ppm which moved to 5.54 ppm on acetylation), an acetate, and a 2-methylbutyrate. Spin decoupling experiments in $CDCl_3$ and C_5D_5N to separate superimposed signals whenever necessary established the presence of partial structure D in which H_d, responsible for a doublet of doublets at 5.82 ppm, was tentatively assigned to the proton under the lactone oxygen and H_e, at 4.12 ppm, to the proton under the hydroxyl. H_e was in turn coupled to a broadened singlet (H_f) at 5.22 ppm, presumably a proton under one of the two ester functions. H_g (doublet at 5.19 ppm), vicinally coupled to H_d, was also allylically coupled to the vinyl methyl resonating at 1.79 ppm; the existence of a strong NOE (18% signal enhancement) showed that the double bond was cis.



D



E

Irradiation of a multiplet at 5.33 ppm simplified multiplets at 2.73 and 2.28 ppm, representing protons which were geminally coupled to each other and vicinally coupled to a third proton resonating at 5.28 ppm. The latter was in turn allylically coupled to the second vinyl methyl responsible for the signal at 1.85 ppm. These results led to partial structure E with a trans double bond because of the absence of an NOE. Combination of D and E then led to the gross structure of formula **4a** which was substantiated by the ^{13}C NMR spectrum and where, because of our failure to obtain homogeneous material from attempts at partial hydrolysis, the distribution of the two ester functions remained uncertain. The lactone ring was trans fused as evidenced by the small values of $J_{6,7}$ and $J_{7,13}$ (2 Hz), typical of H-6β,H-7α heliangolides;[19–21] the small value of $J_{7,8}$ (2 Hz) required that the substituent on C-8 be β orientated. The conclusion that the lactone ring was closed to C-6, a possibility a priori not excluded by the decoupling experiments (vide supra), was supported by the positive Cotton effect, whose sign was in agreement with that of other heliangolides containing a trans-fused lactone ring closed to C-6.[19–24] The values of $J_{2,3}$ corresponded to those of 3-epinobilin;[21] hence, the ester function on C-3 was β oriented.

However, the stereochemistry of the ester function on C-9 could not be derived from the information at hand. If **4a** possesses the same conformation as eupaformonin (**7**, methyls anti),[23] as seems likely, H-8 approximately bisects the angle H_α–C_9–H_β and the observed value of $J_{8,9}$ (~4 Hz) is satisfied by either α or β orientation of the ester function on C-9. In a conformation with the two methyl groups syn, the observed value of $J_{8,9}$ requires an ester on C-9 to be α. A similar situation exists in the case of eupatocunin (**6**),[7] for which $J_{8,9}$ was reported as 3 Hz and where the configuration at C-9 remained indeterminate.[25]

To settle the uncertainty about the distribution of the two ester functions between C-3 and C-8 and the stereochemistry at C-9, an X-ray analysis of **4a** was undertaken. Crystal data are listed in Table III; Figure 2 is a stereoscopic drawing of the molecule which, in view of the positive CD, also represents the absolute configuration of the molecule for the reasons adduced earlier in the case of **1e** (see Table IV for lactone ring torsion angles). The 2-methylbutyrate ester function is attached to C-9 and β, as is the acetate on C-3 and the hydroxyl on C-8. As surmised, the conformation resembles that of eupaformonin, with the C-4 methyl projecting below the plane and the C-10 methyl above the plane of the ten-membered ring. Tables VIII, IX, and X, containing bond lengths, bond angles, and torsion angles, and Tables XIII and XIV, listing final atomic and final anisotropic thermal parameters, are available as supplementary material.

Experimental Section[26]

Extraction of *E. recurvans*. Above the ground parts of *Eupatorium recurvans* Small, collected by Dr. R. K. Godfrey on August 31, 1968, in the pine flatwoods between Cedar Key and Chiefland, Levy Co., Fla. (Godfrey #68143 on deposit in The Florida State University herbarium),[27] wt 20 kg, were extracted with $CHCl_3$ and worked up in the usual fashion[29] to give 180 g of extract. A 100-g amount of the crude extract was chromatographed on 980 g of silicic acid (Mallinckrodt 100 mesh) with solvents of increasing polarity, 500-mL fractions being collected. Elution with benzene and benzene–$CHCl_3$ (fractions 1–58) gave 0.45 g of a crystalline triterpene mixture. Elution of the silicic acid column with $CHCl_3$ (fractions 59–132) gave a gum which was rechromatographed over 150 g of silicic acid ($CHCl_3$) to give a crystalline mixture of **1e** and **4a**, which was separated by LC using an EtOAc–benzene (1:4) solvent system and a Porasil column. Elution of the original silicic acid column with MeOH–$CHCl_3$ (1:24) (fractions 138–144) gave **1a** as the major compound.

Characterization of the Lactones. Lactone **1a**, wt 16 g, mp 185–186 °C, was recrystallized from EtOAc–MeOH: $[\alpha]_D$ +42.3° (*c* 3,01, $CHCl_3$); CD curve $[\theta]_{273}$ −4020; IR bands at 3450, 3430, 1760, 1740, 1650, 1250, 1160, and 1060 cm^{-1}; strong UV end absorption.

Anal. Calcd for $C_{22}H_{30}O_8$: C, 65.55; H, 7.16; O, 30.30; mol wt, 422.1940. Found: C, 65.20; H, 6.93; O, 30.49; mol wt (MS), 422.1927.

Other important mass spectral peaks were at *m/e* 363 ($M^+ - C_2H_3O_2$), 321 ($M^+ - C_5H_9O_2$), 261 ($M^+ - C_2H_3O_2 - C_5H_{10}O_2$), and 243 ($M^+ - C_2H_3O_2 - C_5H_{10}O_2 - H_2O$).

A solution of 0.213 g (6.8×10^{-4} mol) of (±)-α-phenylbutyric anhydride and 0.057 g of **1a** (1.2×10^{-4} mol) in 2 mL of pyridine was allowed to stand at room temperature for 48 h. Excess anhydride was destroyed by adding 2 mL of water and allowing the mixture to stand at room temperature for 12 h. The solution was extracted with ether, and the extract was washed with water, three 10-mL portions of 5% $NaHCO_3$ solution, and again several times with water. The combined aqueous layers were washed with $CHCl_3$, acidified with 1 N H_2SO_4, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried and evaporated; this afforded 0.087 g of α-phenylbutyric acid (pure by TLC criteria), $[\alpha]_D$ −0.87°. This corresponded to an optical yield of 9.2%.

Acetylation of 0.4 g of **1a** with acetic anhydride–pyridine furnished **1b** and **1c**, which were separated by preparative TLC (EtOAC–benzene, 1:1). Yield of gummy **1b**, 0.13 g: IR bands at 3490, 1760, 1740, and 1240 cm^{-1}.

Anal. Calcd for $C_{24}H_{32}O_9$: mol wt, 464.2046. Found: mol wt (MS), 464.2047.

1c, yield 0.21 g, was also gummy and had IR bands at 1760, 1740, and 1240 cm^{-1}.

Anal. Calcd for $C_{26}H_{34}O_{10}$: mol wt, 506.2152. Found: mol wt (MS), 506.2150.

Lactone **1e**, yield 160 mg, had mp 113–114 °C after recrystallization from EtOAc–hexane: $[\alpha]_D$ +52.9° (*c* 0.945, $CHCl_3$); CD curve $[\theta]_{267}$ −2440 (MeOH): IR bands at 3500, 1750, 1730, 1650, 1240, 1145, and 1085 cm^{-1}; strong UV end absorption. The mass spectrum did not exhibit the molecular ion; important peaks were found at *m/e* (% composition) 347 ($M^+ - C_2H_3O_2$, 11.9), 305 ($M^+ - C_5H_9O_2$, 83.2), 263 ($M^+ - C_5H_9O_2 - C_2H_2O$, 56), 262 ($M^+ - C_2H_2O - C_5H_{10}O$, 7.7), 245 ($M^+ - C_2H_4O_2 - C_5H_9O_2$, 54.2), 244 ($M^+ - C_2H_4O_2 - C_5H_{10}O_2$, 16.4), 227 (23), 199 (16.4), 167 ($C_9H_{11}O_3$, 17.6) and 163 ($C_{10}H_{11}O_2$, 43.5).

Anal. Calcd for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44; O, 27.55. Found: C, 64.86; H, 7.34; O, 27.59.

Acetylation of 20 mg of **1e** with acetic anhydride–pyridine gave **1f** as a gum: IR bands at 1750, 1730, and 1250 cm^{-1}. The low-resolution mass spectrum exhibited diagnostic peaks at *m/e* 448 (M^+), 389 ($M^+ - C_2H_3O_2$), 347 ($M^+ - C_5H_9O_2$), and 227 ($M^+ - 2C_2H_4O_2 - C_5H_9O_2$).

Anal. Calcd for $C_{24}H_{32}O_8$: mol wt, 448.2097. Found: mol wt (MS), 448.2097.

Lactone **4a**, wt 85 mg, had mp 129–131 °C after recrystallization from EtOAc–hexane: $[\alpha]_D$ −82.0° (*c* 1.26, $CHCl_3$); CD curve $[\theta]_{264}$ +1250 (MeOH); IR bands at 3420, 1730, 1650, 1235, 1140, and 1055 cm^{-1}; strong UV end absorption.

Anal. Calcd for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44; O, 27.55; mol wt, 406.1990. Found: C, 64.86; H, 7.34; O, 27.40; mol wt (MS), 406.1951.

Other significant peaks in the high-resolution mass spectrum were at *m/e* (% composition) 347 ($M^+ - C_2H_3O_2$, 18.0), 305 ($M^+ - C_5H_9O_2$, 100), 263 ($M^+ - C_2H_2O - C_5H_9O_2$, 11.1), 262 ($M^+ - C_2H_2O - C_5H_{10}O_2$, 14.3), 261 ($M^+ - C_2H_3O - C_5H_{10}O_2$, 3.5), 245 ($M^+ - C_2H_4O_2 - C_5H_9O_2$, 24), 244 ($M^+ - C_2H_4O_2 - C_5H_{10}O_2$, 21), 227 ($M^+ - C_2H_3O_2 - C_5H_{10}O_2 - H_2O$, 18.7), 226 ($M^+ - C_2H_4O_2 - C_5H_{10}O_2 - H_2O$, 11.6), 199 ($C_{14}H_{15}O$, 19.3), and 166 ($C_9H_{10}O_3$, 30.7).

Acetylation of 20 mg of **4a** with acetic anhydride gave **4b** as a gum. The low-resolution mass spectrum exhibited diagnostic peaks at *m/e* 448 (M^+), 389 ($M^+ - C_2H_3O_2$), 347 ($M^+ - C_5H_9O_2$), and 227 ($M^+ - 2C_2H_4O_2 - C_5H_9O_2$).

Oxidation of 1a. A solution of 0.100 g of **1a** in 10 mL of anhydrous ether was stirred at room temperature with 0.100 mg of activated MnO_2, the reaction being followed by TLC. After 4 days, the mixture was filtered and the precipitate washed with ether. The combined filtrate and washings were evaporated, and the residue was purified by preparative TLC (MeOH–$CHCl_3$, 1:19). The major band yielded 80 mg of starting material. A less polar minor band yielded aldehyde **1d** as a gum whose mass spectrum exhibited significant peaks at *m/e* 420 (M^+), 361 ($M^+ - C_3H_2O_2$), 319 ($M^+ - C_5H_9O_2$), 276 ($M^+ - C_5H_9O_2 - C_2H_3O_2$), and 241 ($M^+ - C_2H_3O_2 - C_5H_{10}O_2 - H_2O$).

Oxidation of 1b. To a solution of 0.100 g of **1b** in 10 mL of acetone cooled to 0 °C was added dropwise with stirring Jones reagent until the solution remained red. Stirring was continued for an additional 30 min, at which time excess reagent was destroyed by addition of 2-propanol. After filtration, the filtrate and washings were evaporated; preparative TLC of the residue yielded 15 mg of **2a**, 20 mg of **2b**, and 25 mg of **3** as gums. The IR spectrum of **2a** had bands at 1770 and 1750 cm^{-1}.

Anal. Calcd for $C_{24}H_{30}O_{10}$: mol wt, 478.1839. Found: mol wt (MS), 478.1840.

Other significant peaks in the mass spectrum were at *m/e* 419 ($M^+ - C_2H_3O_2$), 377 ($M^+ - C_5H_9O_2$), 376 ($M^+ - C_5H_{10}O_2$), and 316 ($M^+ - C_5H_{10}O_2 - C_2H_4O_2$).

The IR spectrum of **2b** had bands at 3490, 1760, 1740, and 1730 cm^{-1}.

Anal. Calcd for $C_{19}H_{22}O_9$: mol wt, 394.1264. Found: mol wt (MS), 394.1267.

Other significant peaks in the mass spectrum were at *m/e* 335 ($M^+ - C_2H_3O_2$), 334 ($M^+ - C_2H_4O_2$), and 274 ($M^+ - 2C_2H_4O_2$).

The IR spectrum of **3** had bands at 3490, 1760, and 1745 cm^{-1}.

Anal. Calcd for $C_{24}H_{32}O_{10}$: mol wt, 480.1995. Found: mol wt (MS), 480.1994.

X-Ray Analysis of 1e. Intensity data were measured on a Hilger-Watts automatic form circle diffractometer (Ni-filtered Cu Kα radiation, θ–2θ scans, pulse height discrimination). The size of the crystal used for data collection was approximately 0.5 × 0.5 × 0.7 mm. There were 1725 independent reflections for $\theta < 57°$, of which 1628 were considered to be observed [$I > 2.5\sigma(I)$]. The structure was solved by a multiple solution procedure[30] and was refined by full matrix least squares. In the early stages of refinement it became apparent that C-19 of the isovalerate (see Figure 1, C-4′ in the usual numbering) was disordered. Atom C-19 was replaced by two atoms, C-19A and C-19B, with occupancy factors of 0.75 and 0.25, respectively. With these occupancy factors, the isotropic temperature factors for the two partial atoms were about the same. C-20 serves as the terminal methyl carbon for both C-19A and C-19B. In the final refinement, anisotropic thermal parameters were used for all carbon and oxygen atoms except C-19B and isotropic temperature factors were used for C-19B and the hydrogen atoms. The hydrogen atoms were not refined. The final unweighted and weighted *R* values were 0.057 and 0.079 for the 1628 observed reflections. There were no peaks on the final difference map greater than ±0.2 e/A^{-3}.

X-Ray Analysis of 4a. The size of the crystal used for data collection was approximately 0.15 × 0.20 × 0.9 mm. Of the 1520 independent reflections for $\theta < 57°$, 1306 were considered to be observed. The structure was solved by the multiple solution procedure and was refined by full matrix least squares. Anisotropic thermal parameters were used for the heavier atoms and isotropic temperature factors for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices were $R = 0.051$ and $R_w = 0.057$ for the 1306 observed reflections. There were no peaks greater than ±0.2 e/A^{-3} on the final difference map.

Extraction of Other *Eupatorium* Species. Chloroform extracts of a previously studied[31] collection of *E. leptophyllum* DC. did not furnish a significant quantity of sesquiterpene lactone fraction; neither did two collections of *E. compositifolium* Walt. (Godfrey #61643 and 67964) nor additional collections of previously studied[32,33] *E. capillifolium* (Lam.) Small and *E. pinnatifidum* Ell.[34]

Registry No.—**1a**, 66922-25-6; **1b**, 66922-26-7; **1c**, 66922-27-8; **1d**, 66922-28-9; **1e**, 66922-29-0; **1f**, 66922-35-8; **2a**, 66922-30-3; **2b**, 66922-31-4; **3**, 66922-32-5; **4a**, 66922-33-6; **4b**, 66922-34-7; (±)-α-phenylbutyric anhydride, 66922-36-9; (−)-α-phenylbutyric acid, 938-79-4.

Supplementary Material Available: Tables V–XIV listing bond lengths, bond angles, torsion angles, final atomic parameters, and final anisotropic thermal parameters of compounds **1e** and **4a** (12 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Work at The Florida State University was supported in part by a grant (CA-13121) from the U.S. Public Health Service through the National Cancer Institute.

(2) Recipient of a grant from the Belgian Commission for Educational Exchange with the U.S.A. and a Fulbright-Hayes Travel Award.

(3) W. Herz and R. P. Sharma, *J. Org. Chem.*, **41,** 1015, 1021 (1976). These papers also contain references to earlier work on *Eupatorium* species.

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(7) Our negative results on *E. compositifolium* are in agreement with ref 6c.

(8) Identification of the lactone ring terminus with H_d and the proton under one of the ester side chains with H_e was based on chemical and solvent shifts in a number of related compounds.

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(13) The generalization[19] that $J_{7,13}$ in heliangolides < 3 Hz does not hold for heliangolides possessing a 9,10 double bond.

(14) The values of $J_{1,2a}$ and $J_{1,2b}$ listed in Table I for **1a–e** do not unambiguously distinguish between α and β orientation of the hydroxyl group on C-1.

(15) A. T. McPhail and G. A. Sim, *Tetrahedron,* **29,** 1751 (1973).

(16) A. F. Beecham, *Tetrahedron,* **28,** 5543 (1972).

(17) This is evident from a drawing[12a] showing the conformation of eupacunin *o*-bromobenzoate as well as from diagrams of the crystal structures of this substance and eupacunoxin *m*-bromobenzoate kindly furnished by Professor G. A. Sim. The planar representations of these compounds and of their congener eupacunolin by Kupchan and co-workers are somewhat confusing as they show a β-orientated hydroxyl group on C-1, although the hydroxyl group is actually α with respect to the plane of the ten-membered ring. The confusion results from depicting C-1 as a reentrant carbon atom, which our planar formulas **1** and **5** avoid. For comments on the problem of representing germacranolides and suitable conventions, see D. Rogers, G. P. Moss, and S. Neidle, *J. Chem. Soc., Chem. Commun.* 142 (1972).

(18) Small samples of eupacunin (**5a**), eupacunoxin (**5b**), and eupatocunin (**6**) were supplied by the Developmental Therapeutics Program, Chemotherapy, National Cancer Institute. Unfortunately, they were not sufficiently pure enough (due to polymerization) to permit the measurement of their CD's for the purpose of establishing their absolute configurations by comparison with the CD's of **1a** and **1e** (for eupacunin and eupacunoxin) and **4a** (for eupatocunin). The chemical shifts and coupling constants exhibited by **5a** and **5b** were essentially identical with those of **1e** in the same solvent (except for the protons of the ester side chain).

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(24) We wish to thank Dr. M. Holub for providing us with unpublished details on the CD curves of nobilin, 3-epinobilin, 1(10)-epoxynobilin, and eucannabinolide. $[\theta]_{\max}$ for these and other heliangolides containing an α,β-unsaturated ester side chain occurs at shorter wavelengths than in **4a,** presumably because in these cases the observed CD curves represent the summation of two superimposed Cotton effects, one due to the inherently asymmetric unsaturated lactone chromophore and the second due to the inherently symmetric but asymmetrically perturbed unsaturated ester chromophore.

(25) The NMR spectrum of crude eupatocunin (see ref 18) at 270 MHz was not sufficiently well resolved to permit analysis. However, it seems very likely that its stereochemistry at C-9 is identical with that of **4a.**

(26) Experimental procedures are those of W. Herz, A. Srinivasan, and P. S. Kalyanaraman, *Phytochemistry,* **14,** 233 (1975).

(27) *E. recurvans* Small is a diploid whose distribution is limited to Florida.[34] Our present material is different from a collection of *E. "recurvans"* (Godfrey #67977) which we identified as a naturally occurring hybrid of *E. recurvans* and *E. rotundifolium* in an investigation of its flavonol glycosides[28] and which can now be referred to as *E. mohrii* Greene (private communication from Dr. R. K. Godfrey).

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(32) W. Herz, S. Gibaja, S. V. Bhat, and A. Srinivasan, *Phytochemistry,* **11,** 2859 (1972).

(33) Plants grouped under the name *E. pinnatifidum* are temporary diploid hybrids or hybrid segregates of strikingly distinct morphology with *E. perfoliatum* as one parent and *E. capillifolium* or perhaps *E. compositifolium* as the other.[35] The plant material duplicates that of the collection previously[28,32] referred to as *E. capillifolium* x *perfoliatum.*

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