

# NEW GERMACRANOLIDES FROM *CALEA TERNIFOLIA* AND THE MOLECULAR STRUCTURE OF 9 $\alpha$ -HYDROXY-11,13-DIHYDRO-11 $\alpha$ ,13-EPOXYATRIPLICIOLIDE-8 $\beta$ -O-[2-METHYLACRYLATE]

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**ABSTRACT.**—*Calea ternifolia* var. *calyculata* yielded the new sesquiterpene lactones 9 $\alpha$ -acetoxyzexbrevin (1) and 9 $\alpha$ -hydroxy-11,13-dihydro-11 $\alpha$ ,13-epoxyatripliciolide-8 $\beta$ -O-[2-methylacrylate] (4). Their structures were characterized by <sup>1</sup>H nmr and mass spectral methods and the molecular structure of the latter compound was determined by single crystal x-ray diffraction.

*Calea ternifolia* var. *ternifolia* contained a mixture of two known calein-type compounds as well as a crystalline mixture of the known 9 $\alpha$ -hydroxy-11,13-dihydro-atripliciolide-8 $\beta$ -O-[2-methylacrylate] (3) and 9 $\alpha$ -hydroxy-11,13-dihydro-11 $\alpha$ ,13-epoxyatripliciolide-8 $\beta$ -O-[2-methylacrylate] (4). Single crystal x-ray data of a mixture of 3 and 4 were obtained.

In our biochemical systematic study of the tribe Heliantheae (Compositae) (1) we have initiated an extensive biochemical systematic investigation of members of the taxonomically complex genus *Calea* of the subtribe Galinsogineae (2, 3). Previously, a number of furan-type heliangolides represented by 3 and their biogenetic precursors and derivatives have been isolated from various *Calea* species but also from other taxa of the tribe Heliantheae (4-10). We wish to report the structures of the new germacranolides from *Calea ternifolia* HBK var. *calyculata* (B. L. Robinson) Wussow & Urbatsch and *C. ternifolia* HBK var. *ternifolia* from Mexico.

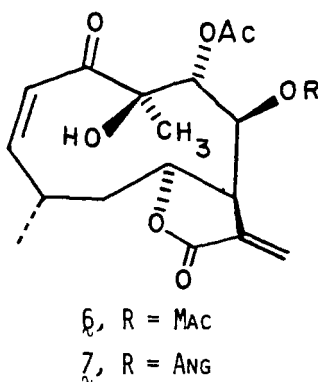
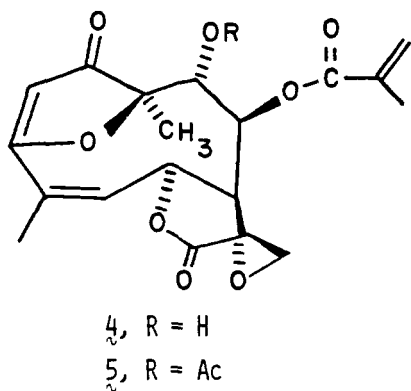
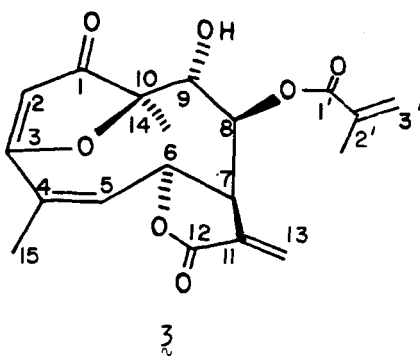
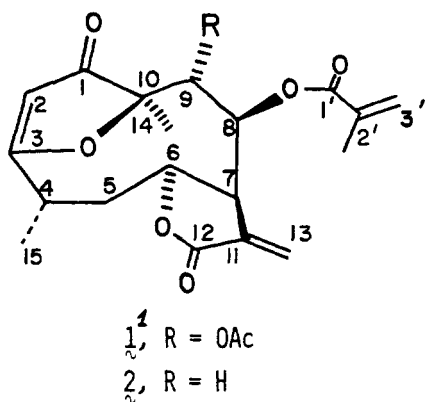
The new compounds were characterized by chemical and spectral methods, and the molecular structures of 4 as well as a mixture of 3 and 4 were determined by single crystal X-ray diffraction.

## RESULTS AND DISCUSSION

### *Chemical and Spectroscopic Characterizations*

**9 $\alpha$ -Acetoxyzexbrevin (1).** This crystalline compound, C<sub>21</sub>H<sub>24</sub>O<sub>8</sub>, mp 200-3°, was isolated from *C. ternifolia* var. *calyculata*. The <sup>1</sup>H nmr spectrum exhibited absorptions which were very similar to zexbrevin (2) (7, 9) except that spin decoupling experiments on 1 indicated only one C-9 proton with a chemical shift (5.38 ppm) that suggested an ester function at C-9. A three-proton singlet at 2.20 ppm together with a mass spectral peak at *m/z* 43 was in agreement with an acetate moiety in 1. Since the chemical shift of the acetate methyl was the same as in a zexbrevin-type compound obtained from a 9 $\alpha$ -hydroxy precursor by acetylation (11), we tentatively assigned the attachment of the acetate to C-9 and the methacrylate to C-8. The coupling *J*<sub>7,8</sub> ≈ 1 Hz suggested an 8 $\alpha$ -H (10), and *J*<sub>8,9</sub> = 5 Hz correlated well with a H-9 $\beta$  or a 9 $\alpha$ -acetoxy group in 1, as derived from stereomodel considerations.

**9 $\alpha$ -Hydroxy-11,13-dihydro-11 $\alpha$ ,13-epoxyatripliciolide-8 $\beta$ -O[2-methylacrylate] (4).**—*Calea ternifolia* var. *calyculata* provided a colorless crystalline compound which we named 9 $\alpha$ -hydroxy-11,13-dihydro-11 $\alpha$ ,13-epoxyatripliciolide-8 $\beta$ -O-[2-methylacrylate] (4), C<sub>19</sub>H<sub>20</sub>O<sub>8</sub>, mp 200° (dec). The uv ( $\lambda$  max 262 nm) and ir (1700 and 1590 cm<sup>-1</sup>) absorptions suggested a furenone carbonyl chromophore (12). The presence of hydroxyl(s) and a  $\gamma$ -lactone moiety was indicated by ir bands at 3415 and 1785 cm<sup>-1</sup>, respectively, and an absorption at 1705 cm<sup>-1</sup>



<sup>1</sup>The stereochemistry of C-10 as shown in the above sesquiterpene lactone structures has in the past caused considerable problems in the literature (8). Since in the above representations C-10 adopts a reentrant position the configuration is shown with a C-10 $\alpha$ -methyl group although it holds a C-10 $\beta$ -methyl in the actual three-dimensional structure. In all compounds (1 to 7) the chirality at C-10 is *R*. See page 59 in reference 4 for a more detailed discussion of this problem.

suggested an additional ester function. This was assigned a methacrylate ester on the basis of diagnostic <sup>1</sup>H nmr signals (two one-proton broadened singlets at 5.66 and 5.94 and a broad three-proton singlet at 1.91 ppm) as well as ms peaks at *m/z* 290 (M-C<sub>4</sub>H<sub>6</sub>O<sub>2</sub>) and 69 (C<sub>4</sub>H<sub>5</sub>O). The <sup>1</sup>H nmr spectral pattern was in agreement with a furan-type heliangolide skeleton related to 9 $\alpha$ -hydroxyatripliciolide-8 $\beta$ -O-[2-methylacrylate] (1) (13). However, signals typical for the exocyclic methylene lactone protons near 6 ppm were missing. Instead, two one-proton signals appearing as doublets (AB-pattern) were found near 3.6 ppm suggesting oxygen(s) at C-11 and C-13. Acetylation of compound 4 provided a monoacetate (5), C<sub>21</sub>H<sub>22</sub>O<sub>9</sub>, which lacked a hydroxyl-absorption in the ir spectrum. This indicated the presence of only one hydroxyl function in 4 which, on the basis of detailed double resonance experiments (table 1), must be attached to C-9, thus excluding a possible C-11,C-13-glycol moiety. Alternatively, the presence of an 11,13-epoxide function was in agreement with the empirical formula and the <sup>1</sup>H nmr parameters of the known compound 3 (13). The data of the new germacrano- lide (4) established the basic skeletal arrangement of 4 including its stereochemical

TABLE 1.  $^1\text{H}$  Nmr parameters<sup>1</sup> of compounds 1, 4 and 5.

	1 <sup>a</sup>	4 <sup>b</sup>	5 <sup>a</sup>
H-2.....	5.58 brs	5.84 s	5.65 s
H-4.....	3.05 brp (7)	—	—
H-5a.....	2.60 ddd (14,9.5,7)	5.94 brq (2.5)	6.04 m
H-5b.....	2.06 brd (14)	—	—
H-6.....	4.32 dd (9.5,5)	5.35 m	5.05 m
H-7.....	3.62 m	3.99 dd (6.5,2.5)	3.51 dd (6.0;2.2)
H-8.....	4.99 brd (5)	5.32 dd (6.5,2.5)	4.94 dd (6.5;2.2)
H-9.....	5.38 d (5)	4.47 t (6.5)	5.17 d (6.5)
H-13a.....	5.38 d (3.0)	3.59 d (6.5)	3.13 d (6.2)
H-13b.....	6.33 d (3.0)	3.64 d (6.5)	3.34 d (6.2)
C <sub>4</sub> -CH <sub>3</sub> .....	1.39 d (7)	1.90 brs	2.12 brs
C <sub>10</sub> -CH <sub>3</sub> .....	1.38 s	1.77 s	1.46 s
OAc.....	2.20 s	—	2.20 s
C-2'-CH <sub>3</sub> .....	1.88 s	1.91 brs	1.91 brs
H-3'a.....	6.02 brs	6.5 brs	6.04 q (2.2)
H-3'b.....	5.66 brs	5.66 brs	5.74 brs

<sup>1</sup>Spectra were run at ambient temperatures in CDCl<sub>3</sub><sup>a</sup> and d<sub>5</sub>-pyridine<sup>b</sup> at 200 MHz; TMS was used as internal standard. Values are in ppm ( $\delta$ ) and signals are designated as follows: singlets, s; doublet, d; triplet, t; quartet, q; pentet, p; multiplet, m; broad singlet, brs. Figures in parentheses are coupling constants or line separation in hertz.

centers except at C-11. Definitive structural data of compound 4 including the chiral center C-11 were obtained by single crystal X-ray diffraction.<sup>2</sup>

#### X-Ray Diffraction Data of 4.

Bond distances are given in table 2, bond angles in table 3, and some selected torsion angles in table 4. All are within accepted ranges. The crystal structure of 4 unambiguously confirms the basic skeletal arrangement and relative stereochemistry of all chiral centers and establishes the epoxide at C11-C13 to be  $\alpha$ -oriented. The epoxide stereochemistry is the same as that found in stramonin-B, in which the  $\gamma$ -lactone ring is *cis*-fused at C6-C7 (14). This difference in fusion mode apparently has small effects upon the geometry of the epoxy lactone. The five-membered ring of the present study is somewhat more planar (average torsion angle magnitude 7.0°) than that of stramonin-B (16.2°), and several bond distances differ significantly [C11-C13, 1.465(4); C11-O8, 1.451(3); C11-C12, 1.488(4) Å vs. 1.444(3), 1.425(3), and 1.512(3) Å, respectively, for stramonin-B].

The portion of the molecule containing the furenone chromophore and adjacent *cis*-double bond at C4-C5 is strikingly similar to that found in eremantholide-A (12). All distances, angles, and torsion angles in this fragment of the two molecules are indistinguishable. The dihedral angle formed by the furenone ring and the plane of the double bond (C3/C4/C5/C6/C15) is 86.1°, as compared to 85.6° in eremantholide-A. The angle between the planes of the 2,3-double bond and 4,5-double bond of nearly 90° does not allow extended conjugation of the C-1 carbonyl chromophore and is the reason for the low wavelength uv absorption near 260 nm (12).

No close intermolecular contacts exist; particularly, the hydroxyl substituent at C-9 does not engage in hydrogen bonding with any of the several potential acceptors. All H...H contacts are greater than 2.4 Å, H...C or O > 2.58 Å, and all intermolecular contacts between heavy atoms are greater than 3.2 Å.

<sup>2</sup>After completion of our work on *Calea ternifolia*, a publication (6) appeared describing the isolation and structure determination of a compound from *Calea pilosa* which appears to be identical with 4. Although the compound described by Bohlmann *et al.* (6) was a gum and compound 4 is crystalline (mp 200°) their  $^1\text{H}$  nmr parameters seem to indicate that the two substances are identical. The two structural assignments differ in the stereochemistry at C-11 in which Bohlmann *et al.* had tentatively assigned a C-11 $\beta$ -epoxy function based mainly on  $^1\text{H}$  nmr data. Since X-ray data of compound 4 showed a C-11 $\alpha$ -epoxide group the 11,13-epoxylactones described in the literature (6) will most likely have the reverse configuration at C-11.

TABLE 2. Interatomic distances (Å) and their standard deviations.

Atoms	Distance	Atoms	Distance
C1-O4	1.225(3)	C9-O7	1.422(3)
C1-C2	1.434(3)	C9-C10	1.531(3)
C1-C10	1.527(3)	C10-O3	1.450(3)
C2-C3	1.339(3)	C10-C14	1.521(3)
C3-C4	1.479(3)	C11-C12	1.488(4)
C3-O3	1.360(2)	C11-C13	1.465(4)
C4-C5	1.319(4)	C11-O8	1.451(3)
C4-C15	1.504(3)	C12-O2	1.205(3)
C5-C6	1.506(3)	C12-O1	1.335(3)
C6-C7	1.555(3)	C13-O8	1.442(4)
C6-O1	1.462(3)	C16-O5	1.343(3)
C7-C8	1.557(3)	C16-O6	1.204(3)
C7-C11	1.504(3)	C16-C17	1.491(3)
C8-C9	1.539(3)	C17-C18	1.402(4)
C8-O5	1.449(2)	C17-C19	1.391(4)

TABLE 3. Bond angles (°) and their standard deviations.

Atoms	Angle	Atoms	Angle
C10-C1-O4	123.4(2)	C9-C10-C14	112.5(2)
C10-C1-C2	105.7(2)	C1-C10-C14	111.6(2)
C2-C1-O4	130.9(2)	C1-C10-O3	103.8(2)
C1-C2-C3	107.8(2)	C14-C10-O3	108.7(2)
C2-C3-O3	114.3(2)	C7-C11-C12	108.0(2)
C2-C3-C4	132.5(2)	C7-C11-C13	126.2(3)
O3-C3-C4	112.5(2)	C7-C11-O8	118.3(2)
C3-C4-C5	116.2(2)	C12-C11-C13	122.1(3)
C3-C4-C15	118.4(3)	C12-C11-O8	113.3(2)
C5-C4-C15	125.4(3)	C13-C11-O8	59.3(2)
C4-C5-C6	122.2(2)	C11-C12-O1	109.8(2)
C5-C6-C7	116.9(2)	C11-C12-O2	128.3(3)
C5-C6-O1	108.3(2)	O1-C12-O2	121.9(3)
O1-C6-C7	106.8(2)	C11-C13-O8	59.9(2)
C6-C7-C8	116.5(2)	O5-C16-O6	121.6(2)
C6-C7-C11	102.4(2)	O5-C16-C17	112.9(2)
C8-C7-C11	113.7(2)	O6-C16-C17	125.5(2)
C7-C8-C9	115.3(2)	C16-C17-C18	119.6(2)
C7-C8-O5	114.9(2)	C16-C17-C19	116.1(2)
C9-C8-O5	106.4(2)	C18-C17-C19	124.2(2)
C8-C9-C10	118.4(2)	C6-O1-C12	111.8(2)
C8-C9-O7	105.9(2)	C3-O3-C10	107.4(2)
C10-C9-O7	109.3(2)	C8-O5-C16	117.0(2)
C9-C10-C1	112.2(2)	C11-O8-C13	60.9(2)
C9-C10-O3	107.7(2)		

TABLE 4. Selected torsion angles (°).

Atoms	Angle	Atoms	Angle
C10-C1-C2-C3	-2.1	C9-C10-O3-C3	109.7
C1-C2-C3-C4	165.6	C6-C7-C11-C12	-10.5
C2-C3-C4-C5	-87.2	C7-C11-C12-O1	9.9
C3-C4-C5-C6	5.4	O1-C6-C7-C11	7.9
C4-C5-C6-C7	-70.5	C11-C12-O1-C6	-4.6
C5-C6-C7-C8	121.7	C12-O1-C6-C7	-2.3
C6-C7-C8-C9	-112.5	C1-C2-C3-O3	-4.3
C7-C8-C9-C10	64.3	C2-C3-O3-C10	9.1
C8-C9-C10-C1	58.7	O3-C10-C1-C2	7.0
C9-C10-C1-C2	-109.0	C7-C8-O5-C16	73.7
C10-O3-C3-C4	-162.9	O5-C16-C17-C18	-18.3

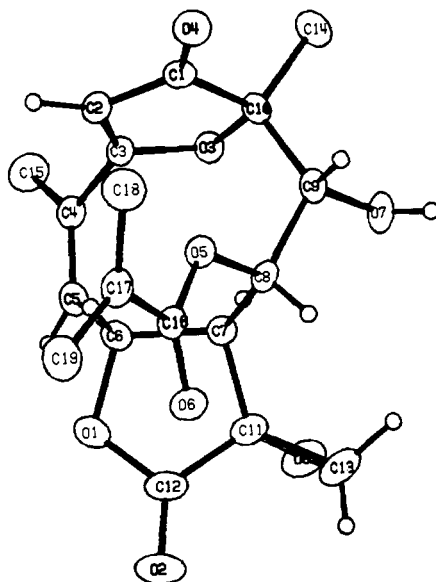


Figure Caption: The  $\beta$ -face of 9 $\alpha$ -hydroxy-11,13-dihydro-11 $\alpha$ ,13-epoxyatripliciolide-8 $\beta$ -O-[2-methyl-acrylate] (4). Hydrogen atoms of methyl groups and of the methacrylate substituent have been omitted for clarity.

## EXPERIMENTAL

**PLANT MATERIAL.**—*Calea ternifolia* var. *calyculata* (3) (syn. *Calea salmaefolia*) October 14, 1980, in Mexico: Nuevo Leon, along the highway to Iturbide; 14.2 miles west of General Hospital on the west edge of Linares. (J. Wussow No. 278). *Calea ternifolia* var. *ternifolia* (3) (syn. *Calea pringlei*) was collected on October 25, 1980, in Mexico: Guerrero along Highway 55, 4.8 miles northwest of the junction with Highway 95 to Taxco. (Wussow-Landry No. 344). Vouchers are deposited at the Herbarium of Louisiana State University at Baton Rouge, Louisiana, U.S.A.

**EXTRACTION.**—Dried leaves (405 g) of *C. ternifolia* var. *calyculata* were extracted and worked up according to a standard procedure (15) to yield 11.7 g of crude syrup. The syrup was chromatographed over 230 g silica gel; 100 ml fractions were taken. Petroleum ether was used as an eluent followed by petroleum ether-ethyl acetate mixtures (90:10, 80:20, 70:30, etc.). Fractions 14 and 15 provided 100 mg of 7-O-methyl acacetin (16); fractions 18 and 19 contained 110 mg of 1; and fractions 20-23 gave crude lactonic material which upon rechromatography yielded 48 mg of pure crystalline 4.

Dried aerial parts of *C. ternifolia* var. *ternifolia* (630 g) provided 15 g of crude syrup. Column chromatography followed by plc gave the known compounds 6 (200 mg) (7,8,13) and 7 (690 mg) (5,7,13), the lactone 3 (71 mg) (13), and a crystalline mixture of 3 and 4 (640 mg). The identity of compounds 6 and 7 was established by comparison of their  $^1\text{H}$  nmr parameters with data reported in the literature (7,8).

9 $\alpha$ -Acetoxyzexbrevin (1),  $\text{C}_{21}\text{H}_{24}\text{O}_8$ , mp 200-203° (Et $_2\text{O}$ ); uv,  $\lambda$  max (EtOH), 208 nm ( $\epsilon$   $2.34 \times 10^3$ ), 258 ( $\epsilon$   $1.39 \times 10^3$ ); cd, (c,  $4.95 \times 10^{-4}$ , MeOH):  $[\theta]_{217}^{25} - 2.3 \times 10^3$ ,  $[\theta]_{258}^{25} + 1.3 \times 10^3$ ,  $[\theta]_{310}^{25} 2.5 \times 10^3$ ; ir,  $\nu$  max 1767 ( $\gamma$ -lactone), 1759 (ester), 1715 (unsaturated ester), 1698 (ketone), 1593 (enolic double bond); ms (ei),  $m/z$  (rel. int.): 404.1470 (.5,  $\text{M}^+$ ), 318.1102 (1.3,  $\text{M}-\text{C}_4\text{H}_6\text{O}_2$ ), 259.096 (.3,  $\text{M}-\text{C}_6\text{H}_8\text{O}_4$ ), 125.1 (45.8,  $\text{C}_7\text{H}_9\text{O}_2$ ), 69.1 (100.0,  $\text{C}_4\text{H}_5\text{O}$ ), 41.2 (15.2,  $\text{C}_2\text{H}_5$ ).

Anal. calcd. for  $\text{C}_{21}\text{H}_{24}\text{O}_8$ : 404.1470. Found: (ms) 404.1470.

9 $\alpha$ -Hydroxy-11,13-dihydro-11 $\alpha$ -13-epoxyatripliciolide-8 $\beta$ -O-[2-methylacrylate] (4),  $\text{C}_{19}\text{H}_{20}\text{O}_8$ , mp 200° (EtOAc), uv,  $\lambda$  max (EtOH), 197 nm ( $\epsilon$   $2.0 \times 10^4$ ), 262 ( $\epsilon$   $1.20 \times 10^4$ ); cd, (c,  $5.19 \times 10^{-4}$ , MeOH):  $[\theta]_{215}^{25} + 3.7 \times 10^3$ ,  $[\theta]_{235}^{25} + 1.1 \times 10^3$  (maximum),  $[\theta]_{260}^{25} + 4.2 \times 10^3$  (minimum),  $[\theta]_{267}^{25} + 5.1 \times 10^3$  (maximum),  $[\theta]_{293}^{25} + 1.6 \times 10^3$  (minimum),  $[\theta]_{315}^{25} + 3.4 \times 10^3$  (maximum); ir,  $\nu$  max 3415 (OH), 1785 ( $\gamma$ -lactone), 1705 (ester), 1698 (ketone), 1587  $\text{cm}^{-1}$  (enolic double bond); ms (ei),  $m/z$  376 (14.7,  $\text{M}^+$ ), 360 (.9,  $\text{M}-\text{O}$ ), 290 (2.2,  $\text{M}-\text{C}_4\text{H}_6\text{O}_2$ ), 69 (100,  $\text{C}_4\text{H}_5\text{O}$ ).

Anal. calcd. for  $\text{C}_{19}\text{H}_{20}\text{O}_8$ : 376.1157. Found (ms): 376.1171.

Acetate (5). Acetylation of 30 mg of 4 in 1 ml pyridine and 1 ml of  $\text{Ac}_2\text{O}$  for 2 hr followed by the usual work-up gave 17 mg of acetate (5); mp 57-60°; ir,  $\nu$  max ( $\text{CHCl}_3$ ), 1798 ( $\gamma$ -lactone), 1760, 1720 (esters), 1700 (ketone), 1598 $^{-1}$  (double bond); ms (ei),  $m/z$  418 (11.7,  $\text{M}^+$ ), 402 (.4,  $\text{M}-\text{O}$ ), 69 (100,  $\text{C}_4\text{H}_5\text{O}$ ), 43 (18.3,  $\text{C}_2\text{H}_5\text{O}$ ), 41 (15.3,  $\text{C}_2\text{H}_5$ ).

**SINGLE CRYSTAL X-RAY DIFFRACTION DATA FOR COMPOUND 4.**—Crystals of 4 were grown in

ethyl acetate as large, colorless cubes. A fragment of dimensions 0.52 x 0.48 x 0.26 mm, cut from a larger, well-formed crystal, was used for data collection. Measurements were made with MoK $\alpha$  radiation on an Enraf-Nonius CAD4 automatic diffractometer equipped with a graphite monochromator.

*Crystal Data:* C<sub>19</sub>H<sub>20</sub>O<sub>8</sub>, MW=376.4, orthorhombic space group P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>,  $a=9.863(2)$ ,  $b=10.022(1)$ ,  $c=18.420(3)$  Å,  $Z=4$ ,  $d_c=1.373$  g cm<sup>-3</sup>,  $\lambda=0.71073$  Å,  $\mu(\text{MoK}\alpha)=1.16$  cm<sup>-1</sup>. Intensity data were measured with  $\omega$ -2 $\theta$  scans of variable speed, designed to yield  $I\sim 50\sigma(I)$  for all significant reflections. Background measurements were made at the beginning and end of each scan, and the intensities were corrected for background. Periodic remeasurement of standard reflections indicated an 11.5% decay in intensities during data collection, for which corrections were applied. Of the 1842 data in one octant having  $4^\circ\leq 2\theta\leq 50^\circ$ , 1530 had  $I>\sigma(I)$  and were used in the structure solution and refinement.

The structure was solved by direct methods program MULTAN (17), completed by Fourier techniques, and refined by full-matrix least squares to  $R=0.033$ . All hydrogen atoms were located in difference maps, and all but those of methyl group C(14) and of the methacrylate substituent were refined. Coordinates for nonhydrogen atoms can be obtained from one of the authors (N.H.F.).

Initially, crystals from *Calea ternifolia* var. *ternifolia* were subjected to X-ray analysis and found to consist of a mixture of the epoxide (4) and its parent methylene lactone (3), which crystallize isomorphously, in an epoxide/methylene ratio of approximately 1.8:1. These crystals have only slightly different cell dimensions from those of the pure epoxide:  $a=10.003(4)$ ,  $b=10.028(3)$ ,  $c=18.325(4)$  Å. The structure was refined to  $R=0.077$  based upon 1025 observed data. Although this structure is much less precise, due to the poorer quality of the crystals and the substitutional disorder, it exhibits no significant differences from the structure of the pure epoxide.

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