chloroacetone with aniline. Ethyl oxanilate (9) was prepared[20] by the reaction of diethyl oxalate with aniline. Satisfactory spectroscopic data have been obtained on all compounds.

Piperylenes were distilled and stored at −5 °C. Benzophenone was used as obtained from the Tokyo Kasei Co. Absolute alcohols were prepared in the usual way just before use. All other reagents were obtained from commercial sources and used as received.

Irradiations for Product Identification. In a typical run, a solution of **1a** (1.0 g) in methanol (150 mL) was placed in a Pyrex well equipped with a thermometer and a water-cooled condenser. A high-pressure, 300-W, Hg lamp with a water-cooled quartz jacket was used as an external light source. The reaction vessel and light source were immersed in a water bath. The progress of the reaction was monitored by removal of aliquots with a syringe and examination by TLC. After irradiation for 16.5 h, the irradiation mixtures were concentrated on a rotary evaporator and chromatographed on a 2.0 × 30 cm silica gel (Woelm, activity III) column with chloroform as eluant to afford methyl benzoate (0.139 g, 22.7%), methyl benzoylformate (0.047 g, 6.4%), and dichloroacetophenone (0.051 g, 6.0%) which had the same NMR spectra and GC retention times as authentic samples.

Irradiation for Analytical Purposes. All irradiations outlined in Tables I–III and Figures 1 and 2 were carried out on 25-mM solutions of 1 in alcohol in a Pyrex tube of 5.0-mL capacity at 25 °C. The progress of reaction was monitored by GC analysis of aliquots removed from the irradiation mixture. The irradiation was generally interrupted at about 30% completion in order to minimize error associated with the product decomposition. The identity of the products was confirmed by GC comparison with authentic samples prepared as above.

Sensitized irradiations were conducted by using a Ritsu MC-20 radiating monochromator (250-W xeonon arc lamp) so as to assure absorption of most of incident light by the photosensitizer. Thus, when sensitized irradiation was carried out in Pyrex tubes containing 131 mM benzophenone ($\epsilon \sim 70$ at 366 nm) and 25 mM **1a** ($\epsilon \sim 0.7$ at 366 nm) with light of 366-nm wavelength from the monochromator, more than 98% of the incident light was absorbed by the sensitizer.

For quenching studies, a stock solution of 1 in methanol was prepared, and 3-mL portions were added to Pyrex tubes containing varying amounts of piperylene. The tubes were then corked and placed in the "merry-go-round" for irradiation.

Degassing was accomplished by subjecting the samples to a minimum of three freeze–degas–thaw cycles at a pressure near 10^{-5} mmHg. A purge of the samples with the gas (N_2 or O_2) was carried out at 0 °C with vigorous stirring by a magnetic stirring bar.

Irradiation of Trichloroacetanilide (7) in Ethanol. A solution of 7 (1.0 g) in ethanol (150 mL) was irradiated and worked up as described above to afford ethyl *N*-phenylcarbamate (8; 15.8 mg, 2.5%) and ethyl oxanilate (9; 213.5 mg, 28.4%). GC analysis of the reaction mixture showed that aniline (12.3%) was present as a major byproduct.

Attempted Irradiation of Other Trichloroacetyl Compounds. Irradiation of hexachloroacetone (25 mM) in nondegassed methanol in a quartz tube was carried out with the unfiltered 300-W Hg lamp. GC monitoring of the reaction indicated that neither methyl trichloroacetate nor methyl trichloropyruvate was detected even after more than 70% of the starting material was consumed. Similar irradiation of methyl trichloroacetate resulted in no detection of methyl carbonate or methyl oxalate.

Registry No. **1a**, 2902-69-4; **1b**, 36930-95-7; **1c**, 27704-37-6; **2a**, 93-58-3; **2b**, 99-75-2; **2c**, 1126-46-1; **3a**, 15206-55-0; **3b**, 34966-53-5; **3c**, 37542-28-2; **4a**, 2648-61-5; **4b**, 4974-59-8; **4c**, 5157-57-3; **7**, 2563-97-5; **8**, 101-99-5; **9**, 1457-85-8; aniline, 62-53-3.

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Unusual Germacranolides from *Inula eupatorioides*[1]

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Three new germacranolides, ineupatolide, ineupatorolide A, and ineupatorolide B, were isolated from *Inula eupatorioides* DC. Structures were deduced by chemical transformations and X-ray crystallography. The absolute configurations are discussed.

The sesquiterpene lactones so far found in *Inula* species (tribe Inuleae, Compositate)[2-4] are relatively simple germacra-1(10),4,5-dien-8,12-olides or substances formed from them by cyclization and subsequent scission processes which have been adumbrated elsewhere.[5,6] Best known are alantolactone and its congeners from several *Inula* species including *I. helenium* (elecampane), an article of commerce. We now report isolation from *I. eupatorioides*

(1) Work at the Florida State University was supported in part by a United States Public Health Service grant (CA-13121) through the National Cancer Institute.
(2) Fischer, N. H.; Olivier, E. J.; Fischer, H. D. *Fortschr. Chem. Org. Naturst.* **1979**, *38*, 47, ref 97, 111, 115, 163, 259, 560, 583, 583a, 768–773, 847, 850e, 921, 1003.
(3) Mukhametzhanov, M. N.; Abdrakhmanov, O. A.; Adekenov, S. N. *Teor. Osn. Pererab. Miner. Org. Syr'ya* **1976**, *3*, 104; *Chem. Abstr.* **1979**, *91*, 123889.
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(5) Herz, W. *Isr. J. Chem.* **1977**, *16*, 32.
(6) Seeming exceptions to the rule that lactone ring closure toward C-8 prevails in *Inula* (as it generally does in *Inulinae sensulato*) are germanin from *I. germanica*,[7] several herbolide A analogues among the plethora of lactones in *I. helenium*[8] and *I. royleana*,[8] and 8-hydroxyeremanthin in *I. aschersonia*.[9]
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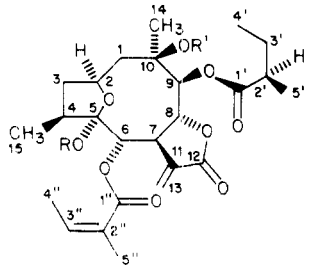
Table I. ^{1}H NMR Spectra Data[a]

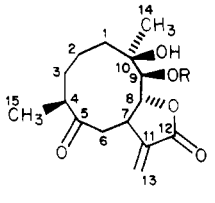
	1a	2a	2c	4c	5	6	7
H-1	1.51 m[b]	*b*	*b*	*b*	*b*	*b*	2.46 t (5.5)
H-2	4.37 sextet (7)	*b*	*b*	*b*	*b*	*b*	*b*
H-3	2.58 m, 1.76 m	1.76 m[c]	1.76[c]	*b*	*b*	*b*	*b*
H-4	2.34 ddq (11.5, 8.5, 7)	2.88 ddq (11, 3, 7)	2.89 ddq	3.00 ddq	2.90 ddq (10, 3.5, 7)	2.98 ddq	2.46 ddq
H-6	5.10 d (8)	2.68[d]	2.69[d]	2.8[d]	2.79[c]	2.61[c]	2.90[c]
H-7	3.89 m (8, 6, 3, 3)	3.63 m (4.5, 2, 3, 2.5, 2)	3.60 m	2.87 m	3.19 m[e]	2.98 m	2.98 m
H-8	4.73 dd (6, 5.5)	4.54 dd (6.5, 3)	4.57 dd (7, 3)	4.69 d (8)	5.31 d (9.5)	4.57 dd (9.5, 1.5)	4.36 dbr (5)
H-9	5.14 d (5.5)	4.67 d (6.5)	4.74 d (7)	3.3		4.03 d (9.5)	9.65 br
H-13a	6.21 d (3)	6.39 d (2.5)	6.40	3.71[f]	3.76[f]	3.72[f]	3.71[f]
H-13b	5.56 d (3)	5.78 d (2)	5.78 d (2)				
H-14	1.39	1.18	1.18	1.23	1.37	1.39	2.16
H-15[g]	1.05 d (7)	1.15 d	1.14 d	1.13 d	1.09 d	1.12 d	1.12 d
H-2′	2.48 sextet (7)	2.48 sextet (7)					
H-3′	1.76 m, 1.51 m	1.76 m, 1.52 m	3.14 q (5.5)				
H-4′[g]	0.97 t (7.5)	0.98 t	1.44 d (5.5)				
H-5′[g]	1.27 d (7)	1.22 d	1.62				
misc	*h*			3.33[g] (OMe), 2.56 m (H-11)	3.40[g] (OMe), 2.64 m (H-11)	3.40[g] (OMe), 2.5 m (H-11), 1.43[i]	3.32[g] (OMe), 2.54 m (H-11)

[a] Structures numbered with reference to formulas 1 and 3 for ease of comparison. Run at 270 MHz in $CDCl_3$ with Me_4Si as internal standard. Chemical shifts are in parts per million; figures in parentheses are coupling constants in hertz. [b] Signal obscured or in low-field multiplet. [c] Two-proton intensity. [d] Center of AB part of ABx system; J_{AB} = 14.5 Hz, J_{AX} = 11.5 Hz, J_{BX} = 3 Hz. [e] $J_{7,11}$ = 12 Hz, $J_{7,8}$ = 9.5 Hz. [f] Center of AB part of ABX system; J_{AB} = 9–10 Hz, J_{AX} = 3.5–4 Hz, J_{BX} = 5.6 Hz. [g] Intensity three protons. [h] Angeloyl residue: H-3, 6.20 ppm, qq (7, 1.5); H-4, 2.01 ppm, dq (7, 15);[g] H-5′, 1.94 ppm, br.[f] [i] Six-proton intensity; methyls of acetonide.

DC. of three somewhat more complex germacranolides, ineupatolide (**1a**), ineupatorolide A (**2a**), and ineupatorolide B (**2b**). Complete structure elucidation involved use of crystallographic techniques, but the absolute configurations of the new compounds require further study.



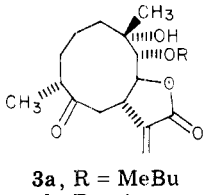
1a, R = R′ = H
b, R = Ac; R′ = H
c, R = H; R′ = Ac



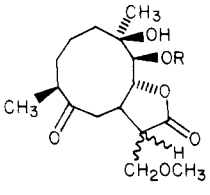
2a, R = MeBu
b, R = Ang

c, R =

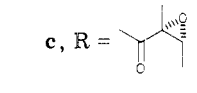
d, R =



3a, R = MeBu
b, R = Ang



4a, R = MeBu
b, R = Ang
c, R = H



c, R =

Table II. ^{13}C NMR Spectral Data of *I. eupatorioides* Constituents[a]

carbon	1a	2a[b]	2b[b]
1	47.96 t	35.43 t	35.43 t
2	71.59 d[c]	*e*	*e*
3	40.76 t	33.69 t	33.84 t
4	44.51 d[d]	41.06 d	41.06 d
5	105.92	215.34	215.34
6	73.94 d[d]	50.74 t	50.74 t
7	45.52 d[c]	45.02 d	44.97 d
8	77.26 d[c]	76.54 d[d]	76.63 d[d]
9	80.26 d[d]	*d, f*	*d, f*
10	73.06	73.32	73.27
11	134.13	137.72	137.64
12	169.39	168.86	168.98
13	125.61 t	123.78 t	123.78 t
14	25.23 q	24.67 q	24.50 q
15	13.99 q	20.44 q	19.77 q
1′	176.61	176.55	167.58
2′	41.06 d	41.06 d	126.76
3′	26.51 t	26.38 t	139.84 d
4′	11.68 q	11.65 q	20.44 q
5′	16.76 q	16.68 q	15.80 q
1″	166.07		
2″	126.71		
3″	141.18 d		
4″	20.35 q		
5″	15.89 q		

[a] Run at 67.9 MHz in $CDCl_3$ with Me_4Si as internal standard. Values are in parts per million. Unmarked signals are singlets. [b] Values from 60:40 mixture of 2a and 2b. [c] Assignments confirmed by single-frequency off-resonance spin decoupling. [d] Assignments may be interchanged. [e] Not detected. [f] Superimposed on $CHCl_3$ signal.

That ineupatolide (**1a**; mp 195–196 °C, $C_{25}H_{36}O_9$) from the more polar fractions of the $CHCl_3$ extract was an α-methylene γ-lactone (IR band at 1765 cm^{-1}) containing angeloyl (Ang) and 2-methylbutanoyl ester side chains (IR bands at 1725 and 1715 cm^{-1}) was apparent from the ^{1}H and ^{13}C NMR spectra (Tables I and II). Spin decoupling

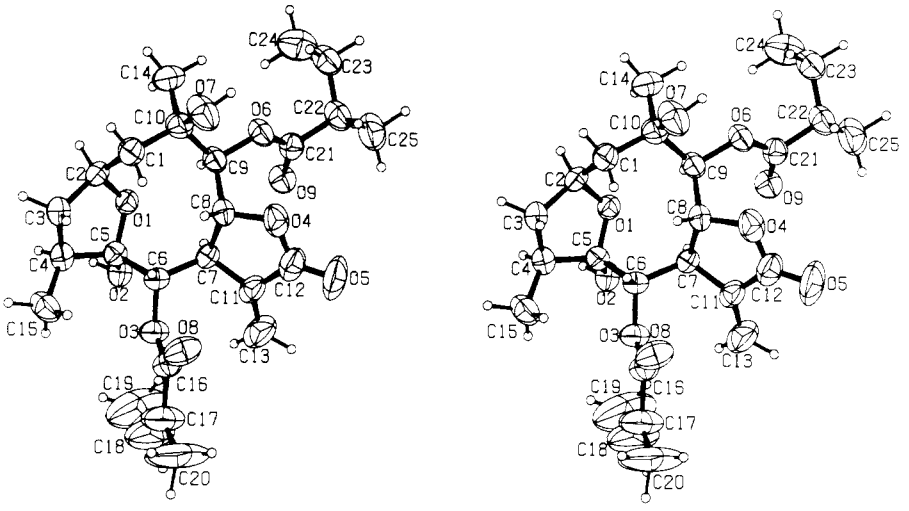
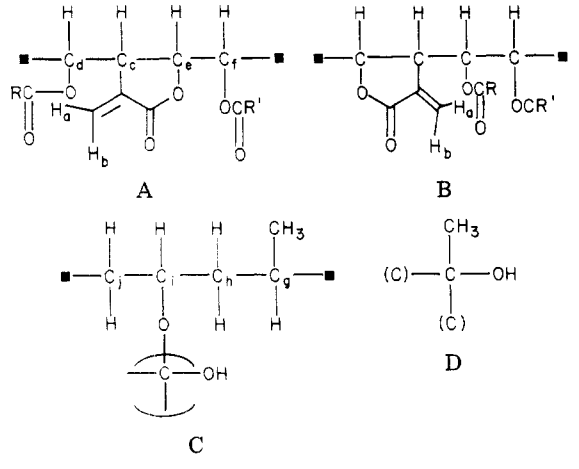


Figure 1. Stereoscopic view of **1a**.

using the narrowly split signals of the vinyl protons (H_a and H_b) near 6.2 and 5.6 ppm as points of departure established the presence of partial structure A or B with preference given to A because of the relative chemical shifts of H_d (5.10 ppm) and H_e (4.73 ppm). Attempts at selective hydrolysis to ascertain the distribution of the two ester functions over C_d and C_f in A (or C_e and C_f in B) failed.

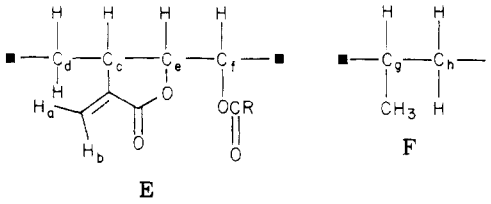


Spin decoupling also revealed the presence of partial structure C; the oxygen atom attached to C_i (doublet at 71.59 ppm) was judged to be that of a cyclic ether in spite of the somewhat unusual paramagnetic shift of H_i (4.37 ppm) as the new lactone was not readily oxidized by Cr(VI) and as acetylation, while successful, was not accompanied by a significant downfield shift of this signal.[10] If so, the appearance in the ^{13}C NMR spectrum of a singlet near 106 ppm suggested that this oxygen was also linked to a quaternary carbon in the form of a hemiketal. The remaining atoms of the molecular formula were represented by D (methyl proton singlet at 1.38 ppm, carbon singlet near 73 ppm).

The most likely structure, deduced by combining A, C, and D, was therefore **1a**, with the relative stereochemistry at C-6, C-7, C-8, and C-9 fixed as shown by the coupling constants but with the allocation of the ester functions to C-8 and C-9 undetermined. In view of the unusual nature of this formula, the several uncertainties involved in arriving at it, and the scarcity of material, the structure was solved by X-ray crystallography. Crystal data are given in the Experimental Section. Figure 1 is a stereoscopic view of the molecule which confirms that the hemiketal linkage across the ten-membered ring involves C-2 and C-5 rather than C-3 and C-10 or C-1 or C-4 as in some heliangolides and that the lactone ring is closed to C-8 and trans fused. The angeloyl group is attached to C-6 and the 2-methylbutanoyl residue to C-8. The absolute configuration, which it was not possible to deduce from the X-ray data, will be discussed in conjunction with that of the ineupatorolides.

In the conformation adopted by the molecule, H-7 is not appreciably deshielded by the ether bridge (as compared with the situation in woodhousin and its analogues). However, it is close to the *syn*-hydroxyl group on C-10 which must account for its chemical shift of 3.89 ppm. The lactone ring is nearly flat, the sum of the internal torsion angles being only 25°. Tables IV–VIII listing final atomic and final anisotropic thermal parameters, bond angles, and selected torsion angles are available as supplementary material.

The less polar fraction from the $CHCl_3$ extract of *I. eupatoroioides* was an inseparable noncrystalline 3:2 mixture of ineupatorolides A and B. Both compounds were α-methylene γ-lactones and had the same basic carbon skeleton but differed in the nature of the single ester side chain, one an α-methylbutyrate and the other an angelate, as shown by mass spectrometry and the ^1H and ^{13}C NMR spectra (Tables I and II). Spin decoupling in the usual way and ^{13}C NMR spectra also established the presence of partial structures E and F; the remaining



carbons, hydrogens, and oxygens of the molecular formulas were present as partial structure D (IR spectrum, carbon singlet near 73 ppm, methyl singlet at 1.18 ppm), two additional methylenes, and a ketone group (IR band at 1705 cm^{-1}, carbon singlet near 215 ppm). Spin decoupling and the determination of coupling constants was facilitated by epoxidation of the mixture which allowed separation of pure ineupatorolide A (**2a**) from a mixture of ep-

(10) The NMR spectrum suggests that the acetylation product is a mixture of C-5 epimers of **1b** or a mixture of **1b** and **1c** (see Experimental Section).

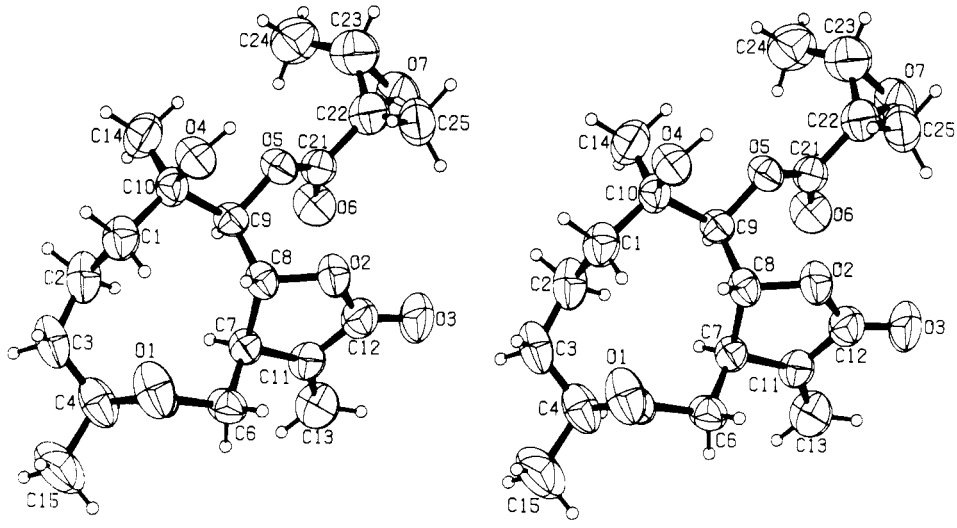
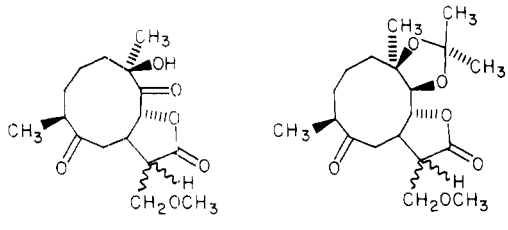


Figure 2. Stereoscopic view of **2c**.

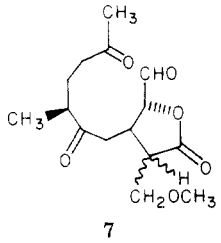
oxyineupatorolides B (**2c** and **2d**). The major epoxidation product **2c** was obtained in crystalline form.

The chemical shifts of the methylene protons of E (AB part of ABX system centered at 2.68 ppm) and the methinyl proton of F (2.88 ppm) made it logical to interpose the ketone group of the ineupatorolides between C_d and C_g. This required placement of partial structure D next to C_f and led, by extension, to the gross formulas depicted in **2a,b** which are not only in accord with the biogenetic isoprene rule but closely resemble that of ineupatolide in functionalization. Additional evidence for the postulated distribution of functional groups on the germacrane skeleton was obtained as follows. Exposure of the ineupatorolide A,B mixture to K_2CO_3–MeOH resulted in formation of mixture **4a,b** by conjugate addition of methanol to the double bond and in hydrolysis to crystalline **4c**. Jones oxidation of the latter gave a diketone, **5**, in whose ^1H NMR spectrum the H-8 signal had



5

6



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collapsed to a sharp doublet at somewhat lower field than that of the doublet of doublets in **4c**, thus locating the new ketone group next to C-8. Compound **4c** also gave an acetonide, **6**, and was cleaved by periodate to secolactone **7**. In the ^1H NMR spectrum of the latter the C-10 methyl signal had moved downfield to 2.16 ppm, a frequency characteristic of a methyl ketone; the signal of H-9 which remained coupled to H-8 was now that of an aldehydic proton at 9.65 ppm. This confirmed the nature and mode of attachment of the potential vicinal glycol system.

Although it was plausible to assume that the stereochemistry of the ineupatorolides was the same as that of ineupatorin, the essentially unrestricted conformational mobility exhibited by Dreiding models of **2a,b** indicated that proof for this hypothesis would be difficult to adduce. Hence, recourse was had to X-ray crystallography. Crystal data for the epoxide **2c** are listed in the Experimental Section. Figure 2 is a stereoscopic drawing of the molecule which shows that the relative stereochemistry is the same as that of ineupatorin and can be depicted in the plane as **2c** (4*S*,7*R*,8*R*,9*S*,10*R*,3′*S*,4′*S*) if Figure 2 also represents the absolute stereochemistry, although it was not possible to deduce this from the X-ray data. The lactone ring is an envelope with C-8 as the flap; the shape of the ten-membered ring does not appear to fit any of the standard cyclodecane conformations.[11] Tables IX–XIII listing final atomic and final anisotropic thermal parameters, bond lengths, bond angles, and selected torsion angles are available as supplementary material.

We conclude by discussing briefly the results of applying to ineupatolide and the ineupatorolides the rules usually employed for deducing absolute configurations of sesquiterpene lactones. The lactone Cotton effect of ineupatolide is positive ($[\theta]_{254}$ +740); if the empirical and sometimes violated rule of Stöcklin, Waddell and Geissman[12] were applicable to germacranolides of this type, Figure 1 (or planar formula **1a**) also represents its absolute configuration (2*S*,4*S*,5*S*,6*S*,7*R*,8*R*,9*S*,10*R*,2*R*′). Beecham's rule[13] which associates the sign of the lactone n,π^* Cotton effect with the chirality of the C=C—C=O chromophore appears to contradict this since in that case the sign of the lactone Cotton effect would be opposite to the sign of the C=C—C=O torsion angle (ω_2 of Table III).[14] Table III also shows that the sign of ω_2, which is very small, is not paired with the sign of ω_3 as is generally the case. This situation has been encountered in some other trans-fused lactones of known absolute stereochemistry,[15-17] and it has

(11) For references, see: Hilderbrandt, R. L.; Wieser, J. D.; Montgomery, L. D. *J. Am. Chem. Soc.* **1973**, *95*, 8598.
(12) Stöcklin, W.; Waddell, T. G.; Geissman, T. A. *Tetrahedron* **1970**, *26*, 2397.
(13) Beecham, A. F. *Tetrahedron* **1972**, *28*, 5543.
(14) It should be noted that for very small values of ω_2, such as have been observed in this instance, only a slight conformational change in going from the crystalline state to solution might be needed to effect a sign reversal of the chromophore angle which in the solid state may be controlled by crystal forces rather than by the ring junction torsion angle.
(15) Sundararaman, P.; McEwen, R. S. *J. Chem. Soc., Perkin Trans. 2* **1975**, 400.

Table III. Lactone Ring Torsion Angles (deg)

atoms[a]	compd 1a	compd 2c
C(8)-O(4, 2)-C(12)-C(11) (ω_1)	3.2	-7.6
O(5, 3)-C(12)-C(11)-C(13) (ω_2)	-0.5	-2.7
C(11)-C(7)-C(8)-O(4, 2) (ω_3)	7.4	-18.4
C(6)-C(7)-C(8)-C(9) (ω_4)	-101.7	-136.8

[a] First number in parentheses next to oxygen atoms refers to numbering in Figure 1 and the second to numbering in Figure 2.

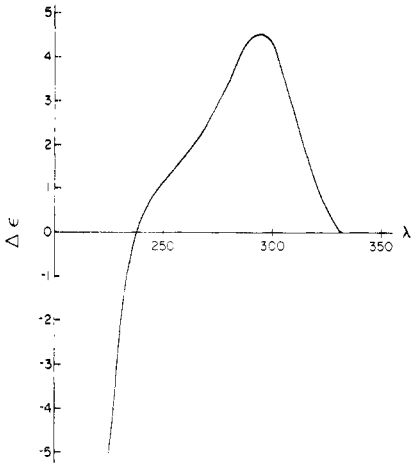

Figure 3. CD curve of epoxyineupatorolide B.

been suggested[16] that the sign of ω_3 (positive if Figure 1 corresponds to the absolute configuration) may provide a better correlation with lactone CD than the sign of ω_2. On this basis, Figure 1 would correspond to the absolute configuration of ineupatolide.

As for the ineupatorolides, the CD curves of these compounds and the derived epoxide (Figure 3) are composites of two positive Cotton effects, the lactone Cotton effect being responsible for a shoulder near 250 nm on the short-wavelength side of a stronger band centered at 294 nm which is due to the n,π^* transition of the ketone. The positive lactone Cotton effect harmonizes with that of ineupatolide and, as in the former case, would be opposite in sign to the sign of the somewhat larger C=C—C=O torsion angle (Table III) if Figure 2 and not its mirror image were to represent the absolute configuration. On the other hand, in the case of epoxyineupatorolide B the sign of ω_3 is actually *paired* with that of ω_2 so that by all rules the absolute configuration should be that of formula **3c**. Additionally, if the solution conformation of epoxyineupatorolide B is little changed from that adopted in the crystalline state, application of the octant rule to Figure 1, which shows the molecule oriented almost perfectly for an octant diagram, predicts a negative ketone Cotton effect for **2c**, primarily because of the axial methyl next to the ketone group, and a positive Cotton effect for the mirror image **3c**, as actually observed. Thus, the absolute configurations of the ineupatorolides would be **3a** and **3b** (4*R*,7*S*,8*S*,9*R*,10*S*), enantiomeric to the absolute configuration **1a** tentatively deduced for ineupatolide. The lack of precedent for such a situation makes unequivocal determination of the absolute configuration by reisolation of **1a** and **2a,b** and X-ray analysis of suitable heavy-atom derivatives highly desirable.[18]

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(17) Herz, W.; Govindan, S. V.; Bierner, M. W.; Blount, J. F. *J. Org. Chem.* **1980**, *45*, 493.

Experimental Section

Extraction of *Inula eupatorioides*. Above-ground parts of *I. eupatorioides* DC. (1.5 kg) collected in the Cherapunje district, Meghalaya, India, were extracted with $CHCl_3$ in a Soxhlet apparatus until the extract was colorless. After removal of $CHCl_3$ at reduced pressure, the residue (40 g) was dissolved in 300 mL of MeOH containing 10% H_2O, allowed to stand overnight, and filtered. The residue was washed with petroleum ether (bp 60–80 °C, 5 × 300 mL), the methanol portion was concentrated at reduced pressure, and the residue was thoroughly extracted with $CHCl_3$. The washed and dried extract was evaporated at reduced pressure, the residue (12 g) was chromatographed over 300 g of silica gel (60–120 mesh, BDH, India), and 200-mL fractions were collected in the following order: fractions 1–6 (Bz–EtOAc, 9:1), 7–12 (Bz–EtOAc, 4:1), 13–18 (Bz–EtOAc, 1:2), 19–24 (Bz–EtOAc, 1:1), 25–30 (Bz–EtOAc, 1:2), 31–36 (Bz–EtOAc, 1:4), 37–42 (EtOAc), 43–48 (EtOAc–MeOH, 99:1), 49–54 (EtOAc–MeOH, 49:1), 54–50 (EtOAc–MeOH, 19:1), 61–66 (EtOH–MeOH, 9:1). Fractions 17–24 (1.2 g) which exhibited one major spot on TLC were combined and purified by preparative TLC (Bz–EtOAc, 4:1) to yield 0.48 g of a gummy mixture of **2a** (60%) and **2b** (40%), as shown by ^1H NMR spectrometry at 270 MHz and high-resolution mass spectrometry. The H-7, H-8, H-9, H-13, and H-14 signals of **2b** differed slightly from those of **2a**; signals of the angeloyl ester side chain were superimposed at 6.16 (br q, J = 7 Hz, H-3′), 2.00 (dq, J = 7, 1.5 Hz, H-4′), and 1.97 ppm (br, H-5′). The mass spectrum showed the molecular ions at m/e 366 and 364 and M^+ − 18 at m/e 348 and 346. Epoxidation of the mixture (0.1 g) in 1 mL of $CHCl_3$ by stirring with *m*-chloroperbenzoic acid at room temperature for several hours, dilution with $CHCl_3$, washing with $NaHSO_3$ solution and water, drying, evaporation, and preparative TLC of the residue (Bz–EtOAc, 4:1) gave 50 mg of pure **2a** and 40 mg of **2c** containing some **2d** (^1H NMR spectrum). The gummy **2a** had the following: IR 3500, 1775, 1730, 1705, 1120 cm^{-1}; CD (MeOH) $[\theta]_{293}$ +9300, $[\theta]_{250}$ ~3000 (sh), $[\theta]_{233}$ −2100 (last reading). The high-resolution mass spectrum exhibited only a very weak molecular ion; other significant mass spectral peaks were at m/e 248 ($C_{20}H_{28}O_5$), 281 ($C_{15}H_{21}O_5$), 264 ($C_{15}H_{20}O_4$), 263 ($C_{15}H_{19}O_4$), 247 ($C_{15}H_{19}O_3$), 246 ($C_{15}H_{18}O_3$), and 85 (C_5H_9O, base peak).

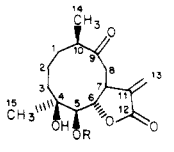
Anal. Calcd for $C_{20}H_{30}O_6$: mol wt 366.2042. Found: mol wt (mass spectrum, peak matching) 366.2042.

Crystallization of the epoxide mixture from EtOAc gave pure **2c**: mp 205–207 °C; IR 3500, 1775, 1730, 1705, 1180, 1150 cm^{-1}; CD (MeOH) $[\theta]_{294}$ +14800 (max), $[\theta]_{250}$ +3600 (sh), $[\theta]_{225}$ −15050 (last reading).

The ^1H NMR spectrum is given in Table I; that of the diastereomeric minor epoxide differed only in the peaks of the ester side chain which are found at 1.41 (d, J = 5.5 Hz, H-4′) and 1.68 ppm (H-5′) and that of H-14 at 1.24 ppm. The high-resolution mass spectrum of **2c** exhibited only a very weak molecular ion; other significant peaks were at m/e (composition, relative intensity) 363 ($C_{20}H_{27}O_6$, 1.9), 264 ($C_{15}H_{20}O_4$, 51.2), 263 ($C_{15}H_{19}O_4$, 100), 247 ($C_{15}H_{19}O_3$, 30.1), 264 ($C_{15}H_{18}O_3$, 20.3), 245 ($C_{15}H_{17}O_3$, 7.3). The low-resolution mass spectrum showed peaks at m/e 380 (M^+), 362, 281, and 263 and the base peak at m/e 99.

Anal. Calcd for $C_{20}H_{28}O_7$: mol wt 380.1835. Found: mol wt (mass spectrum, peak matching) 380.1835.

(18) It might be argued that **3a** and **3b** are members of an enantiomeric series of sesquiterpene lactones with H-7 β, representatives of which have so far not been found in higher plants. Such an objection is invalid. Formulas **3a,b** can be rewritten as **8a,b** which maintain the orientation of H-7 as α but are essentially enantiomeric with **1a** if the distribution of the glycol and ketone functions relative to the lactone ring is used as a criterion. Speculation as to the possible origin of such "enantiomerically-related" lactones is deferred until the absolute configurations of ineupatolide and the ineupatorolides have been established.



8a, R = MeBu
b, R = Ang

Fractions 31–39 (1–3 g) which contained one major constituent were combined and purified by preparative TLC (Bz–EtOAc, 2:1) to give ineupatolide (**1a**) which was recrystallized from EtOAc: yield 0.42 g; mp 195–196 °C; IR 3550, 1765, 1725, 1715, 1650, 1125, 1075 cm^{-1}; $[\alpha]_D$ −18.3° (*c* 0.0503 $CHCl_3$); CD (MeOH) $[\theta]_{254}$ +740 (max), $[\theta]_{234}$ −455 (last reading). The high-resolution mass spectrum displayed only a very weak peak for the molecular ion; other significant peaks were at *m/e* (composition, relative intensity) 462 ($C_{25}H_{34}O_8$, 4.2), 380 ($C_{20}H_{28}O_7$, 1.1), 379 ($C_{20}H_{27}O_7$, 1.7), 378 ($C_{20}H_{26}O_7$, 0.3), 377 ($C_{20}H_{25}O_7$, 7.0), 363 ($C_{20}H_{27}O_6$, 8.3), 305 ($C_{17}H_{21}O_5$, 0.7), 303 ($C_{17}H_{19}O_5$, 13.2), 296 ($C_{15}H_{20}O_6$, 23.2), 278 ($C_{15}H_{18}O_5$, 1.4), 277 ($C_{15}H_{17}O_5$, 1.3), 261 ($C_{15}H_{17}O_4$, 27.4), 260 ($C_{15}H_{16}O_4$, 1.4), 100 ($C_5H_8O_2$, 3.9), 85 (C_5H_9O, 48.8), 83 (C_5H_7O, 100).

Anal. Calcd for $C_{25}H_{36}O_9$: C, 62.49; H, 7.55; mol wt 480.236. Found: C, 62.58; H, 7.75; mol wt (mass spectrum, peak matching) 480.235.

Acetylation of 40 mg of ineupatolide with acetic anhydride–pyridine for 4 days at room temperature followed by the usual workup was still incomplete. Purification by preparative TLC gave starting material and 34 mg of a gum which was homogeneous by TLC criteria but was apparently a mixture of acetates **1b** (epimeric at C-3) or, less likely, a mixture of isomeric acetates **1b** and **1c** on the basis of the ^1H NMR spectrum. The major isomer had signals at 4.48 (m, H-2), 2.68 and 1.49 (m, H-3), 3.27 (m, H-4, compare with H-4 of **1a**!), 5.18 (d, J = 9 Hz, H-6), 3.99 (m, H-7), 4.67 (dd, J = 5.5, 4.5 Hz, H-8), 5.03 (d, J = 4.5 Hz, H-9), 6.22 (d) and 5.57 (d, J = 3 Hz, H-13), 1.38 (d, H-14), and 1.10 ppm (d, J = 7 Hz, H-15) as well as the usual signals of the two ester side chains. The most significant difference in the spectrum of the minor acetate was the chemical shift of H-4 (2.33 ppm, m) which corresponded to that of **1a**; minor displacements occurred in the signals of H-6 (5.21 ppm d), H-8 (4.72 ppm, dd), H-9 (5.13 ppm, d), and H-14 (1.43 ppm). The high-resolution mass spectrum exhibited a peak for the molecular ion of a monoacetate.

Anal. Calcd for $C_{27}H_{38}O_{10}$: mol wt 522.24.65. Found: mol wt (mass spectrum) 522.2448.

$NaBH_4$ reduction of ineupatolide gave a gummy mixture of 11,13-dihydro derivatives as judged by NMR and mass spectrometry. Epoxidiation gave a gummy mixture of diastereomeric epoxyangelates.

Reactions of Ineupatorolides A and B. (a) Catalytic hydrogenation of the ineupatorolide mixture gave a mixture of diastereomeric 11,13-dihydro derivatives of ineupatorolide A as judged by NMR and mass spectrometry. $NaBH_4$ reduction of the ineupatorolide mixture gave, after preparative TLC of the crude product, a mixture of tetrahydro derivatives resulting from reduction of the 11,13 double bond and the 5-ketone group as judged by the NMR and the mass spectrum. (b) A solution of 0.06 g of the ineupatorolide mixture and 0.2 g of anhydrous K_2CO_3 in 5 mL of MeOH was stirred under N_2 for $^1/_2$ h until TLC indicated disappearance of the starting material, diluted with H_2O, acidified with acetic acid, and extracted with $CHCl_3$. The washed and dried extract was evaporated and the residue purified by preparative TLC (EtOAc–Bz 1:1). The less polar gummy fraction (20 mg) was a mixture of **4a,b** (20 mg) which had the following: IR 3500, 1775, 1725, 1710, 1180, 1110 cm^{-1}; mass spectrum, *m/e* 398 and 396 (M^+), 380 and 378 ($M^+ - H_2O$), 295 and 264; ^1H NMR two multiplets in the range 4.65–4.94 (H-8 and H-9), 3.65 (AB system of H-13, 3.34 and 3.31 (OMe of the two components), 3.05 (H-4), 3.05 (m, H-7), 2.82 (AB system of H-6), 2.53 (m, H-11), 1.15 (H-14) and 1.15 ppm (d, H-15), as well as the typical signals of the angeloyl and α-methylbutyryl side chains. The more polar fraction (**4c**, 15 mg) was recrystallized from EtOAc: mp 145 °C; IR 3550, 1775, 1705, 1100 cm^{-1}; mass spectrum, *m/e* 314 (M^+), 296, 278, 264, 246. The ^1H NMR spectrum of this substance is given in Table I.

A solution of 20 mg of the preceding compound in 10 mL of acetone was allowed to stand with 0.1 mL of Jones reagent at 10–15 °C for $^1/_2$ h. After excess reagent was destroyed by addition of MeOH, the mixture was diluted with H_2O and extracted with $CHCl_3$. The washed and dried extract was evaporated, and the residue purified by preparative TLC (Bz–EtOAc, 2:1). Recrystallization from EtOAc afforded **5**: mp 160 °C; IR 3500, 1780, 1730, 1710, 1150, 1100, 1000 cm^{-1}; mass spectrum, *m/e* 312 (M^+), 280, 262, 251. The ^1H NMR spectrum is reported in Table I. A solution of 30 mg of **4c** and one crystal of *p*-toluenesulfonic acid in 4 mL of acetone was allowed to stand overnight and was evaporated in vacuo, and the residue was purified by preparative TLC (Bz–EtOAc, 2:1). This resulted in recovery of 12 mg of starting material and isolation of two products. The more polar gummy fraction was the acetonide **6**: yield 8 mg; IR 1780, 1710, 1100 cm^{-1}. The ^1H NMR spectrum is reported in Table I.

Anal. Calcd for $C_{19}H_{30}O_6$: mol wt 354.2041. Found: mol wt (mass spectrum) 354.2022.

Other significant peaks in the high-resolution mass spectrum were at *m/e* (composition, relative intensity) 339 ($C_{18}H_{27}O_6$, 100), 297 ($C_{16}H_{25}O_5$, 14.6), 296 ($C_{16}H_{24}O_5$, 25), 279 ($C_{16}H_{23}O_4$, 95.4), 247 ($C_{15}H_{19}O_3$, 34.4), 229 ($C_{15}H_{17}O_2$, 34.2).

The less polar fraction (7 mg; IR 1780, 1730, 1705, 1085 cm^{-1}) had the same empirical formula (mass spectrum, *m/e* 354, 339, 307, 297, 296, 265, 251) and appeared to be a C-4 epimer of **6** on the basis of the ^1H NMR spectrum which exhibited signals at 5.18 (dd J = 9.5, 1.5 Hz, H-8), 4.14 (d, J = 9.5 Hz, H-9), 3.71 (AB system of H-13), 3.34 (OMe), 3.04 (dd, J = 12.5, 11 Hz, H-6a), 2.73 (m, H-7), 2.90 (m, J = 1–4 Hz), 2.40 (m, H-6b, superimposed on H-11), 1.47 and 1.39 (methyls of acetonide), 1.34 (H-14), 1.09 ppm (d, J = 6.5 Hz, H-15).

A mixture of 10 mg of **4c** in 2 mL of MeOH and 40 mg of $NaIO_4$ in 0.5 mL of H_2O was allowed to stand overnight at room temperature, diluted with H_2O, and extracted with $CHCl_3$. The washed and dried extract was evaporated in vacuo and purified by preparative TLC (Bz–EtOAc, 2:1). The gummy product **7** was obtained: 6 mg; IR 1775, 1730, 1705, 1180 cm^{-1}; mass spectrum, *m/e* 312 (M^+), 294, 283, 237, 113, 95. The ^1H NMR spectrum is reported in Table I.

X-ray Analyses. Single crystals of ineupatolide were prepared by slow crystallization from acetone–hexane. They were orthorhombic, space group $P2_12_12_1$, with a = 9.100 (3) Å, b = 14.322 (2) Å, c = 19.931 (4) Å, and d_{calcd} = 1.338 g cm^{-3} for Z = 4 ($C_{25}H_{36}O_9$, mol wt 480.55). The intensity data were measured on a Hilger-Watts diffractometer (Ni-filtered Cu Kα radiation, θ–2θ scans, pulse-height discrimination). A crystal measuring approximately 0.3 × 0.4 × 0.6 mm was used for data collection. A total of 2015 reflections were measured for $\theta < 57°$, of which 1941 were considered to be observed [$I > 2.5\sigma(I)$]. The structure was solved by a multiple-solution procedure[19] and was refined by full-matrix least-squares methods. In the final refinement, anisotropic thermal parameters were used for the heavier atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices are R = 0.38 and Rw = 0.047 for the 1941 observed reflections. The final difference map has no peaks greater than ±0.2 e $Å^{-3}$.

Single crystals of epoxyineupatorolide B were prepared by slow crystallization from EtOAc. They were orthorhombic, space group $P2_12_12_1$, with a = 9.675 (4) Å, b = 12.663 (4) Å, c = 16.703 (4) Å, and d_{calcd} = 1.234 g cm^{-3} for Z = 4 ($C_{20}H_{28}O_7$, mol wt 380.44). The procedure used was the same as that in the preceding paragraph with a crystal of approximately 0.15 × 0.20 × 0.5 mm, no absorption correction, and 1598 reflections of which 1414 were considered to be observed. The final discrepancy indices are R = 0.047 and Rw = 0.053 for the 1414 observed reflections. The final difference map has no peaks greater than ±0.2 e $Å^{-3}$.

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Supplementary Material Available: Tables IV and V listing final atomic and final anisotropic thermal parameters for **1a**, Tables IX and X listing these parameters for **2c**, Tables VI, VII, and VIII listing bond lengths, bond angles, and selected torsion angles for **1a**, and Tables XI, XII, and XIII listing the same parameters for **2c** (11 pages). Ordering information is given on any current masthead page.

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