Cyclotagitinin C and Its Transformations[1†]

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The stereochemistry previously assigned to cyclotagitinin C (**2a**) has been confirmed. Epoxidation of anhydrocyclotagitinin C (**3**) gave two epoxides. Reaction of the α-epoxide **5** with Lewis acids resulted in epoxide ring opening with retention of configuration and in rearrangement to a diketone, **8**, whose structure was established by X-ray crystallography. Reaction of the β-epoxide **6** with acids resulted in epoxide ring opening with inversion. The results are contrasted with the behavior of epoxycyclodihydroparthenolide **12**. Various other transformations of cyclotagitinin C are reported.

In one of our reports on heliangolide sesquiterpene lactones from the antileukemic extract of *Tithonia diversifolia*[2-5] we briefly mentioned[4] an acid-catalyzed cyclization of tagitinin C (**1**) and its 1(10)-epoxide to a guaianolide which was provisionally formulated as **2a** (see Chart I). As *trans,trans*-1(10),4-germacradienolides or their 1(10)-epoxides normally undergo cyclization to eudesmanolides[8,9] rather than guaianolides, this behavior was somewhat surprising, particularly since it must involve generation of a positive charge next to a carbonyl group and, in the case of the epoxide, anti-Markovnikov opening of an oxirane as well. If it could be verified, this fortuitous entry into the guaianolide series promised access to certain other C-8-substituted sesquiterpene lactones by modification of the initially formed cyclotagitinin C (**2a**) or its dehydration product **3**. In the following we describe the results of experiments which were intended to explore this possibility and resulted in some unusual transformations.

In light of the unexpected cyclization mode of **1** we first adduce evidence for the C-1 stereochemistry previously ascribed[4] to cycloagitinin C since the matter has some bearing on the transformations to be described in the sequel. That H-1 of **2a** is indeed α as assumed earlier was confirmed by the following facts: (1) Long-range spin–spin couplings involving H-1, H-6, and H-15 of **2a** (Table I); $J_{1,6} \approx 1$ Hz, $J_{1,15} \approx 2$ Hz) are paralleled by similar couplings in the ^{1}H NMR spectrum of *O*-acetylisophotosantonic acid lactone (**4b**; $J_{1,6} = 1$ Hz, $J_{1,15} = 1.5$ Hz), indicating that the nature of the ring fusion must be the same. (2) CD curves of **2a**, **4a**, and **4b** all of which exhibit a negative Cotton effect in the n,π^* region and a positive effect in the π,π^* region of the α,β-unsaturated cyclopentenone chromophore are essentially superimposable if allowance is made for the additional presence in **2a** of an α,β-unsaturated lactone chromophore.[10] As inversion of H-1 from α to β is known to effect inversion of the cyclopentenone Cotton effect,[12,13] H-1 of **2a** is α as it is in **4**. (3) In the ^{1}H NMR spectrum of **2a** addition of trichloroacetyl isocyanate (TAI) produces paramagnetic shifts of δ 1.02 and 0.22 in the signals of H-1 and H-14, respectively, indicating that H-1 and 10-OH are cis[14-16]. As the configuration at C-10 is known,[2] H-1 must be α.

The facile dehydration of **2a** to **3** has been reported previously.[4] Epoxidation of **3** with *m*-chloroperbenzoic acid gave the two isomeric epoxides **5** and **6** in approximately equal amounts. Their ^{1}H NMR spectra (Table I) differed principally in the chemical shifts of H-7 whose signal appeared at δ 4.34 in the spectrum of the less polar and at δ 2.92 in the spectrum of the more polar isomer. Hence the less polar product with a greatly deshielded H-7 (cf. H-7 of **2a** at δ 3.43) was assigned formula **5** and the more polar product formula **6**, a conclusion borne out by subsequent work.[18,20]

† This article is dedicated to Ulrich Weiss on the occasion of his 75th birthday January 24, 1983.

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

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(3) Chowdhury, P. K.; Barua, N. C.; Sharma, R. P.; Thyagarajan, G.; Herz, W. *J. Org. Chem.* **1980**, *45*, 535.

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(5) Examination of the voucher specimen of a collection of "*T. tagetiflora*" studied by Pal et al.[6] has confirmed the suspicion expressed by us[2] that the Lucknow workers were actually dealing with *T. diversifolia*. Examination of the voucher specimen of a collection of what was cited as *T. rotundifolia* from Panama[7] showed that it actually was *T. diversifolia* as well (private communication from Mr. John La Duke, The Ohio State University). For other work on sesquiterpene lactones from *T. diversifolia*, see: Calzada, J. G.; Ciccio, J. F. *Rev. Latinoamer. Quim.* **1978**, *9*, 205. Ciccio, J. F.; Castro, V. H.; Calzada, J. G. *Ibid.* **1979**, *10*, 134.

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(10) The lactone chromophore which is expected to produce a negative Cotton effect near 250 nm[11] appears to be responsible for the fine structure in the 240–300-nm region of **2a** (see Experimental Section).

(11) Stöcklin, W.; Waddell, T. G.; Geissman, T. A. *Tetrahedron* **1970**, *26*, 2397.

(12) Büchi, G.; Kauffman, J. M.; Loewenthal, H. J. E. *J. Am. Chem. Soc.* **1966**, *88*, 3403.

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(14) Samek, Z.; Buděšinský, M. *Collect. Czech. Chem. Commun.* **1979**, *44*, 559.

(15) The only other significant shifts (see Experimental Section) are those of H-9b (δ 0.87), presumably α oriented, and H-9a (δ 0.16), as would be expected from the model.[14]

(16) The carbonyl of the 10-acetoxy group in **4** exerts an equally large paramagnetic β effect[17] on H-1 whose signal is found at δ 4.15.

(17) Narayanan, C. R.; Sarma, M. R. *Tetrahedron Lett.* **1968**, 1553.

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Table I. ^{1}H NMR Spectral Data[a]

	2a	2b[b]	2b[c]	2c	2d	5	6	8	8[c]	9	9[c]	10	17	18	19a
H-1	3.32 tdq (4, 1, 1)												3.41 ddq (3, 2, 2)	3.39 br (2,5, 1.5)	2.58[f]
H-2a	2.60[e]	2.91 dd (21, 19)	2.35	3.15 d (18)	2.98 d (19)	2.72 d (19)	2.75 d	2.50 d (18.5)	1.95 d (18)	2.98 d (19)	2.76 d	2.98 d	4.44 d (3)	4.46 d (2.5)	2.98 dd (16, 7)
H-2b		2.63 dd (15, 19)	2.15	2.88 d (18)	2.36 d (19)	2.49 d (19)	2.58 d	2.41 d (18.5)	1.84 d (18)	2.34 d (19)	~1.8	2.28 d			2.81 dd (16, 7)
H-6	5.42 ddq (11, 1, 2)	5.43 ddq (10, 3, 1)	5.52	5.52 d br (11, 1)	5.48 dq (12, 1)	5.34 dq (10, 1.5)	5.46 dq (11, 1)	4.94 d (10.5)	4.53 d	5.52 d	5.30 d	5.68 d br (10, 1)	5.42 d br (11, 2, 2)	5.68 d br (10, 1.5)	5.36 d (8, 5)
H-7	3.43 dddd (11, 3, 2.5, 2)	3.80 ddt (10, 5, 4)	3.48	3.87 dddd (11, 5, 4, 3)	3.79 dddd (12, 4.5, 3.5, 3)	4.34 ddt (10, 5, 3.5)	2.92 dddd (11, 3.5, 3, 2)	3.19 dddd (10, 3.5, 3, 2)	2.2 m	3.21 m	2.61 m	4.09 dt (10, 3)	3.43 d br (11)	3.42 d (10)	3.48 dddd (9, 3, 2.5, 2)
H-8	5.82 br	5.67 dt (5, 9)	5.50	5.63 dt (5, 8)	5.61 dt (4.5, 8.5)	5.70 dt (5, 8)	5.59 dt (2, 3)	5.69 dt (7, 2)	5.50 d br (7, 1)	5.60 dt (5, 8)	5.30 dt	5.78 t (4)	5.81 t br (~4)	5.62 (3.5)	5.77 dt (3, 2)
H-9a	2.38 dd (16, 4)	2.45 dd (16, 9)	1.9	2.50[e]	2.50 dd (14.5, 8.5)	2.69 dd (16, 8)	2.72 dd (17, 3)	2.98 dd (12.5, 7)	2.50 dd	2.45 dd (15, 8)	~2.2	2.62 dd (15, 3)	2.43 dd (15, 3.5)	2.41 dd (15, 3.5)	2.54[f]
H-9b	2.10 dd br (16, 4)	2.21 ddd (16, 9, 2)	1.3?		2.32 dd (14.5, 8.5)	2.14 dd (16, 8)	2.30 dd (17, 3)	2.78 dd (12.5, 2)	1.63 dd (12.5, 1)	2.24 dd (15, 8)	~1.9	~2.0	2.15 dd (15, 4)	2.05[f]	2.02 dd br (14, 3)
H-13a	6.37 d (3)	6.40 d (4)	6.22	6.39 d	6.37 d (3)	6.32 d (3.5)	6.39	6.38 d (3.5)	6.09 d	6.40 d	6.25 d	6.32 d (3.5)	6.41 d (3)	4.19 d (13)	6.43 d (3)
H-13b	5.67 br (2.5)	5.51 d (4)	5.08	5.51 d (3)	5.49 d (3.5)	5.45 d (3.5)	5.64 d	5.58 d	4.99 d	5.51 d	5.09 d	5.63 d (2.5)	5.70 d (3.5)	3.91 d (13)	5.70 d (2.5)
H-14[d]	1.11	1.49 d (1.5)	0.70	1.57	1.46	1.46	1.42	1.48	1.01	1.21	0.60	1.40	1.13	1.08	1.54
H-15[d]	2.00 dd (2, 1)	2.00 dd (4.5, 1)	1.94	1.96 d (1)	1.91 d	2.10 d (1)	2.07 d (1)	1.99 br	1.86 br	1.90 br	1.90 br	1.98 d (1)	2.07 t (2)	2.05 t (1.5)	2.56

[a] Run at 270 MHz in $CDCl_3$ unless otherwise specified. Unmarked signals are singlets. Chemical shifts are given in δ. Coupling constants (in hertz in parentheses) are not given if they correspond to those in the preceding column; signal of H-2′ in range δ 2.51–2.56 sept (7); H-3′ and H-4′ in range δ 1.10–1.16 d (7). [b] $J_{2a,F}$ = 21 Hz, $J_{2b,F}$ = 15 Hz, $J_{15,F}$ = 4.5 Hz, $J_{6,F}$ = 3 Hz, and $J_{9a,F}$ = 2 Hz. [c] Run in C_6D_6; signal at H-2′ is near δ 2.2, and H-3′ and H-4′ are in the range δ 0.91–0.95. [d] Intensity of three protons. [e] Intensity of two protons; center of AB system. [f] Obscured signal.

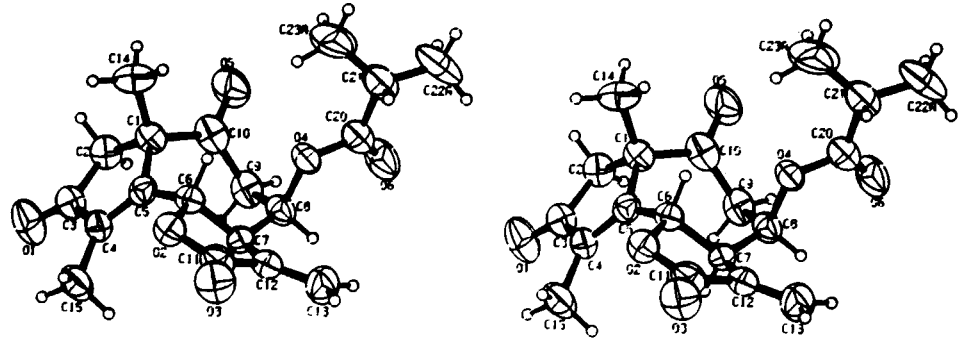
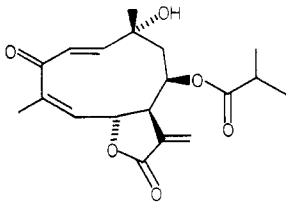


Figure 1. Stereoscopic view of 8 with ellipsoids of thermal motion.

Chart I



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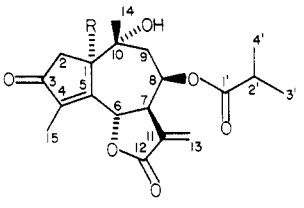
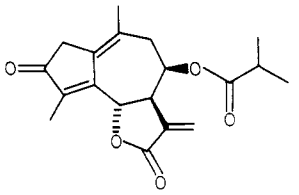


2a, R = H
b, R = F
c, R = Cl
d, R = OH



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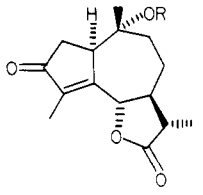
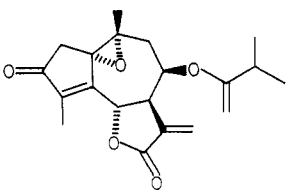


4a, R = H
b, R = Ac



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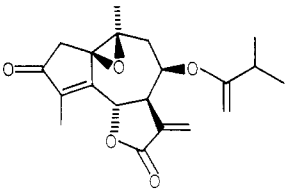

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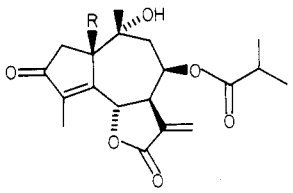
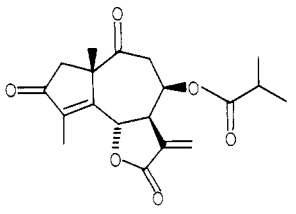


7a, R = F
b, R = Cl
c, R = OH



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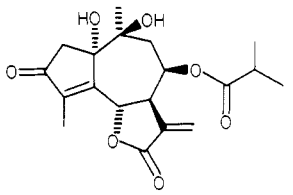


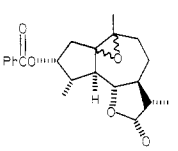
9

The two epoxides displayed marked differences in their behavior toward boron trifluoride etherate. At 0–5 °C **5** gave a fluorohydrin whereas **6** remained unaffected at this temperature. The location of the fluorine atom at C-1 of the fluorohydrin was evident from the ^{1}H NMR spectrum, with H-2a, H-2b, H-6, H-9, and H-15 exhibiting additional couplings of 21, 15, 3, 2, and 4.5 Hz to fluorine. Hence, the oxygen atom was on C-10 and remained α. Substitution of $SnCl_4$ for BF_3 produced the corresponding chlorohydrin; that the hydroxyl group of this substance was also on C-10 and hence α was indicated by the paramagnetic shifts of the signals of H-14 (δ 0.34) and H-9 (δ 0.8) observed in the ^{1}H NMR spectrum after addition of TAI.[14] Formation of the carbamate, however, proceeded much more slowly than in the case of **2a**.

The complete stereochemistry **2b** and **2c** finally assigned to these halohydrins is best considered in conjunction with that of a diol **2d** to which **5** was partially transformed on standing. Because the ^{1}H NMR spectra of these compounds were essentially identical (Table I) except for the additional couplings in **2b** due to fluorine and the chemical shifts of H-2 which are affected by the different substituents on neighboring C-1, it was evident that their stereochemistry was the same. We originally surmised that they were represented by formulas **7a–c** as the result of *trans*-diaxial opening of the epoxide ring. However, the CD curves of the three compounds are essentially superimposable on that of cyclotagitinin C which requires that the C-1 substituent be α, like that in **2a**. The sluggishness with which **2c** and **2d** form TAI derivatives could then be ascribed to steric hindrance in a *cis*-chlorohydrin or *cis*-glycol. The paramagnetic shift of H-7 in **2b–d** ($\Delta\delta$ 0.38–0.44; see Table I) could conceivably be attributed to the α-oriented electronegative substituents on C-1; however, substitution at this position of halogen or hydroxyl for hydrogen also appears to induce a change in the conformation of the seven-membered ring as manifested in the J values involving H-8 and H-9 (Table I; compare **2a** with **2b–d**). Hence the paramagnetic shifts of H-7 in **2b–d** and the upfield shifts of H-7 in the NMR spectra of the **2c** and **2d** TAI derivatives (see Experimental Section) might instead be caused by the greater proximity to H-7 of the α-oriented C-10 hydroxyl in **2b–d** as compared with the situation prevailing in **2a**. That this second explanation is correct was deduced from the spectroscopic properties of **9** (vide infra).

When the reaction of **5** with $SnCl_4$ was carried out at elevated temperature, **2c** was accompanied by a less polar substance, $C_{19}H_{22}O_6$, which was obviously the product of a rearrangement. Of the four possible rearranged carbon skeletons A–D, A and B were eliminated because the substance was neither a methyl ketone nor a β-diketone.

(18) Ando et al.[19] used a chemical shift difference of δ 0.2 for H-6 to distinguish between the α- and β-epoxides of i. The effect of the epoxide ring on H-7 was not noted. In the present instance the chemical shifts of H-6, which is already deshielded by being allylic, were not significantly different.



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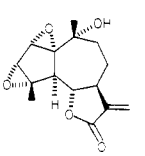
(19) Ando, M.; Akahane, A.; Takase, K. *Chem. Lett.* **1978**, 727. Ando, M.; Akahane, A.; Yamaoka, H.; Takase, K. *J. Org. Chem.* **1982**, *47*, 3909.

(20) Analogously the most significant differences in the ^{13}C NMR spectra (Table II) were the shifts of C-7 (approximately δ 6 upfield in **5**) and C-11 (approximately δ 5 downfield in **5**). Shifts of C-1, C-10, and C-14 differed to a much smaller degree.

(21) A rearrangement similar to the one leading from **5** to **8** was invoked[22] to account for the properties of a substance (iii) formed from canin (ii) on treatment with acetone–sulfuric acid. The disputed structure of canin (chrysartemin B) has recently been confirmed[23] as that proposed originally.[22]



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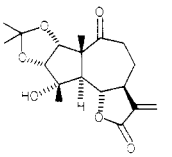


iii

(22) Lee, K. H.; Simpson, R. F.; Geissman, T. A. *Phytochemistry* **1969**, *8*, 1515.

(23) Kelsey, R. G.; Shafizadeh, F.; Campana, C. F.; Craig, R. E. R. *J. Org. Chem.*, in press.

Table VII. Torsion Angles (in Degrees) in 8 with Standard Deviations in Parentheses

C(5)-C(1)-C(2)-C(3)	10.4 (9)
C(1)-C(2)-C(3)-C(4)	-11.1 (9)
C(2)-C(3)-C(4)-C(5)	7.2 (10)
C(3)-C(4)-C(5)-C(1)	0.1 (11)
C(4)-C(5)-C(1)-C(2)	-6.9 (10)
C(1)-C(5)-C(6)-C(7)	-90.7 (8)
C(5)-C(6)-C(7)-C(8)	74.6 (6)
C(6)-C(7)-C(8)-C(9)	-60.9 (7)
C(7)-C(8)-C(9)-C(10)	75.3 (8)
C(8)-C(9)-C(10)-C(1)	-82.4 (7)
C(9)-C(10)-C(1)-C(5)	28.3 (8)
C(10)-C(1)-C(5)-C(6)	49.3 (9)
O(2)-C(6)-C(7)-C(12)	-32.3 (5)
C(6)-C(7)-C(12)-C(11)	24.5 (6)
C(7)-C(12)-C(11)-O(2)	-8.4 (6)
C(12)-C(11)-O(2)-C(6)	-13.4 (6)
C(11)-O(2)-C(6)-C(7)	29.4 (5)
C(6)-C(7)-C(8)-O(4)	57.6 (6)
C(7)-C(8)-O(4)-C(20)	157.8 (6)
C(8)-O(4)-C(20)-C(21)	179.5 (6)
O(4)-C(20)-C(21)-C(22)	170.1 (15), -143.5 (24)
O(4)-C(20)-C(21)-C(23)	-42.9 (21), -1.5 (16)

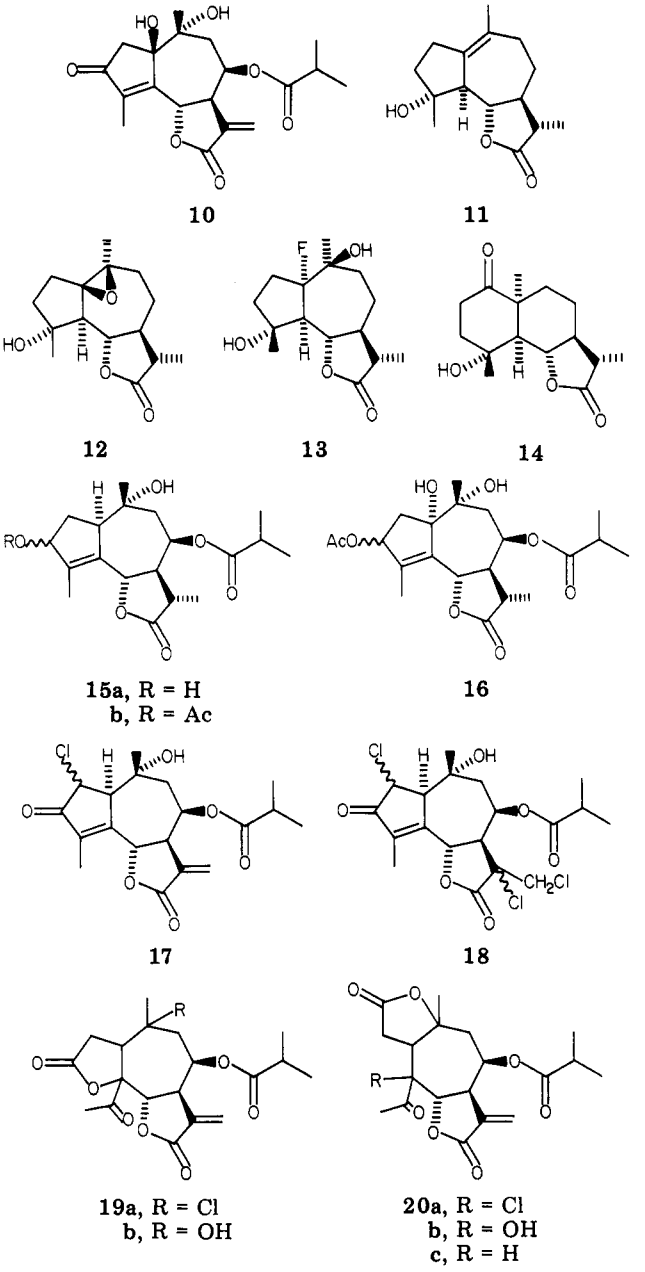
While formula C seemed unlikely because of strain it could not be dismissed out of hand because the ^{13}C NMR spectrum (Table II, supplementary material) displayed a new carbonyl frequency at δ 204.59 in the cyclopentenone range.

To settle the matter and to establish the stereochemistry of the rearrangement product, we undertook an X-ray analysis. Crystal data for the substance are listed in the Experimental Section. Figure 1 is a stereoscopic drawing of the molecule which shows that the substance is of type D and possesses the stereochemistry shown in formula 8. Hence its precursor is indeed the α-epoxide 5 as had been deduced from the spectroscopic evidence.

Tables III–VI listing final atomic and final anisotropic thermal parameters, bond lengths, and bond angles are available as supplementary material. Table VII lists selected torsion angles. As is apparent from these and from Figure 1, the cycloheptane ring approximates a twist–chair whose two-fold axis of symmetry passes through C-1 and the midpoint of the C-7, C-8 bond. Σ_2, the deviation of the ring from C_2 symmetry, is 30°, and $\Sigma_2/\Sigma_s + \Sigma_2$ is 0.18.[24] The cyclopentenone is almost planar with C-2 as the flap of an envelope; the γ-lactone ring is a slightly distorted envelope with C-6 as the flap. The isopropyl group of the ester side chain was disordered. The two methyls were each split into two half-atoms, with the two conformations differing by a rotation of ca. 45° about the C-20, C-21 bond.

As already mentioned, epoxide 6, unlike 5, did not react with BF_3 at 0–5 °C. At room temperature, however, BF_3 treatment of 6 gave a diol, A; an isomeric diol, B, was formed on exposure of 6 to perchloric acid. Neither diol gave a reaction with periodic acid, but diol A reacted immediately with 2 equiv of TAI to form a dicarbamate whereas the C-10 monocarbamoyl derivative initially formed from diol B and TAI reacted only slowly and incompletely to give a dicarbamate.[25] The ^1H NMR spectra of the two diols differed chiefly in the chemical shifts of the H-7 signal, that of A being located at a "normal" frequency of δ 3.20 (cf. H-7 of **2a**) whereas that of B was at δ 4.09. Although a decision between formulas **9** and **10** (Chart II) on this evidence alone would have been difficult, the CD curves resolved the problem. The curve of A exhibited the negative Cotton effect near 320 nm and the positive Cotton effect near 230 nm previously found for **2a–d**, while that of B was enantiomeric. Hence A was **9** and B was **10**.

Chart II



With an α-orientated hydroxyl group on C-1 the seven-membered ring of **9** should have a conformation similar to that of **2b–d**, and, in fact, their distinctive J values involving H-8 and H-9 are also exhibited by **9**. If, as has been suggested earlier, this conformation brings the α-orientated C-10 hydroxyl of **2b–d** closer to H-7 than it is in **2a**, thus accounting for the paramagnetic shift of the H-7 signal, inversion of the configuration at C-10 of **9** should result in restoration of the normal H-7 frequency, as actually observed. On the other hand, in **10**, with the 1-hydroxyl β, the α-orientated hydroxyl on C-10 is in close proximity to H-7 (model) thus accounting for the great paramagnetic shift of H-7.

It is instructive to compare our observations on **3** and its epoxides with the behavior of a somewhat similar

(24) McPhail, A. T.; Sim, G. A. *Tetrahedron* **1973**, *29*, 1751.

(25) Evidence for initial acylation of the hydroxyl group at C-10 was the appearance, within 1 h, of only one NH frequency in the ^1H NMR spectrum accompanied by paramagnetic shifts of the H-14 and H-9 signals, but not of H-2.

guaianolide, 11, formed by cyclization of dihydroparthenolide. Epoxidation of 11 with *m*-chloroperbenzoic acid was reported to produce only one epoxide which was assigned formula 12 because of its rearrangement with BF_3, in low yield, to the fluorohydrin 13 and the *cis*-eudesmanolide 14.[26] Structures of 13[27] and 14[26] were established by X-ray crystallography. Rearrangement of 12 to 14 corresponds to migration of the appositely situated C-1,C-5 bond to a developing charge at C-10 with inversion at the migration terminus, whereas formation of 13 is the result of attack by an external nucleophile (F^-) on C-1. On the other hand, reaction of 6 with BF_3, whatever the mechanism by which OH instead of F is introduced, appears to involve preferential Lewis acid catalyzed cleavage of the C-1,O bond, and C-1,C-5 bond migration toward C-10, although stereoelectronically favorable, is not observed presumably because 6 is a vinylogous α,β-epoxy ketone.[28] However, why reaction of 6 with perchloric acid results in exclusive cleavage of the C-10,O bond is not clear.[29]

In the case of the isomeric vinylogous α,β-epoxy ketone 5, at low temperature nucleophilic attack occurs exclusively at C-1 but with retention, presumably intramolecularly via an epoxide–Lewis acid complex as proposed for halohydrin formation with retention in the case of an ordinary α,β-epoxy ketone.[28b] At elevated temperatures, migration of the C-10 methyl group toward C-1 competes with intramolecular nucleophilic attack by halide, but again there is no evidence for migration toward or nucleophilic attack on C-10.[30,31]

Some additional observations on the chemical behavior of **2a** follow. $NaBH_4$ reduction gave alcohol **15a** characterized as the acetate **15b** which was a single isomer by TLC and NMR criteria. The stereochemistry assigned to C-11 in these compounds is based on the value of $J_{7,11}$ (13 Hz)[32] and the solvent shifts of H-13 ($\delta_{CDCl_3} - \delta_{C_6D_6} = 0.24$ for **15a**, 0.19 for **15b**), which show that the C-11 methyl group is pseudoequatorial.[33] The stereochemistry at C-3 could not be inferred from the J values ($J_{2a,3} = J_{2b,3} = 7.5$ Hz in $CDCl_3$, 8 and 6 Hz in C_6D_6). Oxidation of **15b** with SeO_2 in dioxane produced a *cis*-diol **16** related to **2d** which gave a positive periodate test. This reaction may be generally useful for introduction of functionality at C-1 of the guaianolide skeleton.

As reaction of **2a** with peracids was extremely sluggish, the effectiveness of acid catalysts was explored. In the presence of $SnCl_4$ a monochloroguaianolide, **17**, a trichloroguaianolide, **18**, and a substance with the formula $C_{19}H_{23}O_7Cl$ were formed. Composition and structures of **17** and **18** were obvious from the mass and NMR spectra (Tables I and II); that the hydroxyl group had remained on C-10 and that one chlorine atom was on C-2 and not the reverse was shown by the chemical shifts produced on addition of TAI (see Experimental Section).

As regards the third substance, its IR spectrum, which indicated the absence of a hydroxyl group and had a double strength carbonyl frequency at 1778 cm^{-1} in addition to carbonyl bands at 1735 and 1718 cm^{-1}, its ^{13}C NMR spectrum (Table II), which had carbonyl frequencies near δ 204, 175, 171, and 167 but lacked the vinylic resonances associated with C-4 and C-5 of **2a**, and the ^1H NMR spectrum (Table I) were all consonant with the di-γ-lactone structures **19a** or **20a** resulting from further oxidation and rearrangement of an enol lactone formed by Baeyer–Villiger oxidation of cyclotagitinin C. Mixtures of similar non-halogen-containing dilactones were formed from **2a** in the presence of toluenesulfonic acid as catalyst (see Experimental Section).

Experimental Section

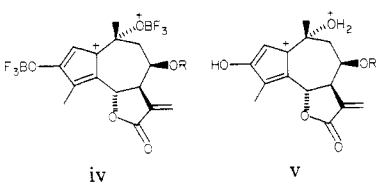
Cyclotagitinin C (2a) and Anhydrocyclotagitinin C (3). Tagitinin C was cyclized to **2a** as described previously and the latter dehydrated to **3** with *p*-toluenesulfonic acid in 55% yield.[2] ^1H and ^{13}C NMR spectra of **2a** are listed in Tables I and II. The CD curve of **2a** (EtOH) had $[\theta]_{323}$ −2760 (negative maximum), $[\theta]_{295}$ −600 (negative minimum), $[\theta]_{271}$ −830 (negative maximum), $[\theta]_{265}$ 0, $[\theta]_{240}$ +27 900 (sh), and $[\theta]_{232}$ +30 900 (positive maximum). This compares with the CD curve of **4b** which had $[\theta]_{320}$ −3400 (negative maximum), $[\theta]_{280}$ 0, and $[\theta]_{232}$ +14 100 (positive maximum), essentially identical with that of **4a**.[13] On addition of trichloroacetyl isocyanate (TAI) under standard conditions,[14] **2** exhibited the following shifts (multiplicities and J values similar to those given in Table I for **2a**): δ 8.28 (NH), 4.24 (H-1), 2.65 (H-2a,b), 5.39 (H-6), 5.39 (H-6), 3.53 (H-7), 5.90 (H-8), 2.54 (H-9a), 2.97 (H-9b), 6.41 and 5.69 (H-13a,b), 1.33 (H-14), 2.03 (H-15).

Epoxidation of 3. A solution of 100 mg of **3** in 20 mL of dry benzene and 40 mg of *m*-chloroperbenzoic acid was kept overnight at room temperature, diluted with 200 mL of CH_2Cl_2, washed with saturated sodium metabisulfite solution, sodium bicarbonate, and water, dried, and evaporated at reduced pressure. The residual gum which showed two major spots on TLC was purified by preparative TLC (benzene–EtOAc, 6:1). The faster moving band contained 30 mg of noncrystalline 1α,10α-epoxy-3-oxo-8β-isobutyroxy-4,11(13)-guaiadien-6α,12-olide (**5**): IR 1770 (γ-lactone), 1730 (ester), 1715 (cyclopentenone), 1650, 1200, 1130, 1110, 1025, 925 cm^{-1}; CD (EtOH) $[\theta]_{331}$ +5400 (sh), $[\theta]_{323}$ +5600 (positive maximum), $[\theta]_{270}$ 0, $[\theta]_{242}$ −19 800 (negative maximum), $[\theta]_{232}$ 0, $[\theta]_{222}$ +16 800 (positive maximum), $[\theta]_{212}$ 0, $[\theta]_{206}$ −14 600 (last reading); ^1H and ^{13}C NMR spectral data are listed in Tables I and II; significant peaks in the low-resolution mass spectrum at m/z 346 (M^+) 276, 258, 243, 240, 230, 216, 188, 167, and 71; mol wt calcd for $C_{19}H_{22}O_6$: 346.1416, found 346.1423 (by peak matching).

The slower moving band contained 35 mg of gummy 1β,10β-epoxy-3-oxo-8β-isobutyroxy-4,11(13)guaiadien-6α,12-olide (**6**): IR 1775, 1730, 1715, 1650, 1200, 1140, 1110, 1025, 920 cm^{-1}; CD (EtOH) $[\theta]_{341}$ −5870 (sh), $[\theta]_{325}$ −9390 (negative maximum), $[\theta]_{317}$ −977 (sh), $[\theta]_{240}$ +35 800 (positive maximum), $[\theta]_{223}$ 0; $[\theta]_{210}$ −27 700 (last reading); ^1H and ^{13}C NMR spectral data are listed in Tables I and II; significant peaks in the low-resolution mass spectrum at m/z 346 (M^+), 276, 258, 243, 240, 230, 216, 187, 137, 121, 71; mol wt calcd for $C_{19}H_{22}O_6$: 346.1416, found 346.1419.

The ^1H NMR spectrum of epoxide **5** samples kept at room temperature indicated gradual alteration. A 30-mg sample of **5** which had been stored in the refrigerator for 6 months showed two major spots, one corresponding to **5** and one of lower R_f. Purification by TLC (silica gel; benzene–EtOAc, 7:3 and 1:1) gave

(26) Fischer, N. H.; Wu-Shih, Y.-F.; Chiari, G.; Fronczek, F. R.; Watkins, S. F. *J. Nat. Prod.* **1981**, *44*, 104.
(27) Fronczek, F. R. *J. Chem. Soc., Perkin Trans. 2* **1979**, 195.
(28) For studies of acid-catalyzed rearrangement of α,β-keto epoxides, see: (a) House, H. O. *J. Am. Chem. Soc.* **1954**, *76*, 1235. (b) House, H. O.; Reif, D. J. *Ibid.* **1955**, *77*, 6525. (c) House, H. O. *Ibid.* **1956**, *78*, 2298. (d) House, H. O. *J. Org. Chem.* **1956**, *21*, 1306. (e) House, H. O.; Wasson, R. L. *J. Am. Chem. Soc.* **1956**, *78*, 4394; **1957**, *79*, 1488. (f) House, H. O.; Reif, D. J.; Wasson, R. J. *Ibid.* **1957**, *79*, 2490. (g) House, H. O.; Reif, D. J. *Ibid.* **1957**, *79*, 6491. (h) House, H. O.; Ryerson, G. D. *Ibid.* **1961**, *83*, 979.
(29) It is possible that coordination of the cyclopentenone carbonyl with a second molecule of Lewis acid (see iv below) is responsible for preferential cleavage of the C-1/oxygen bond of **5** and **6** in the presence of BF_3 and $SnCl_4$ whereas the equilibrium concentration of v in the presence of Brønsted acids is very small.



iv v

(30) Migration of C-2 to C-10 which is favored on stereoelectronic grounds may also be impeded by the strain inherent in C.
(31) Conversion of **5** to diol **2d** could in theory involve nucleophilic attack with retention at either C-1 or C-10. In view of the formation of **2b** and **2c** from **5**, the former possibility appears more likely.

15 mg of **5** and 8 mg of noncrystalline 1α,10α-dihydroxy-3-oxo-8-isobutyroxy-4,11(13)-guaiadien-6α,12-olide (**2d**): ^{1}H NMR spectral data listed in Table I; CD (EtOH) $[\theta]_{313}$ −8200 (negative maximum), $[\theta]_{268}$ −1370 (sh), $[\theta]_{258}$ 0, $[\theta]_{231}$ +54 200 (positive maximum), $[\theta]_{218}$ 0, $[\theta]_{207}$ −53 300 (last reading). On addition of TAI, the ^{1}H NMR spectrum indicated partial formation of two monocarbamates (NH at δ 8.42 and 8.40), one acylated at C-10 (H-14 at δ 1.81) and the other at C-1 (H-14 at δ 1.55). After 6 days, the spectrum indicated the presence of a dicarbamate (NH at δ 8.59 and 8.53) and the two monocarbomates in equal proportions (H-14 in the dicarbamate at δ 1.89 and H-7 and H-6 in the dicarbamate and the monocarbamates at ca. δ 3.35 and 5.31, respectively). The low-resolution mass spectrum did not display significant peaks at m/z higher than 276; in the CI mass spectrum (isobutane) the $M^+ + 1$ ion was the base peak; mol wt calcd for $C_{19}H_{24}O_7$ + H 365.2, found (CI MS) 365.2. Other significant ions in the CI mass spectrum were at m/z (relative intensity) 347 (81), 329 (12), 279 (19), 277 (32), 259 (28), 241 (11), 231 (5), 219 (7), 89 (58), and 71 (21).

Reactions of 5 with Lewis Acids. (a) To a solution of 50 mg of **5** in 0.5 mL of dry dioxane and 2 mL of dry diethyl ether chilled to 0 °C was added 5 drops of freshly distilled boron trifluoride etherate. The mixture was kept in the refrigerator overnight, diluted with 20 mL of ether, washed with $NaHCO_3$ solution and water, dried, and evaporated. Purification of the gummy residue by preparative TLC (benzene–EtOAc, 4:1) gave 30 mg of 1α-fluoro-3-oxo-8β-isobutyroxy-10α-hydroxy-4,11-(13)-guaiadien-6α,12-olide (**2b**) which crystallized on being allowed to stand for several months and was recrystallized from hexane–EtOAc: mp 182.5 °C; IR 3550 (w), 3450 (bonded OH), 1775 (γ-lactone), 1725 (double strength, ester and cyclopentenone), 1655 (w), 1650, 1200, 1130, 1025, 910; CD (EtOH) $[\theta]_{353}$ −850 (sh), $[\theta]_{341}$ −5200 (sh), $[\theta]_{323}$ −8600 (negative maximum), $[\theta]_{318}$ −8350 (negative minimum), $[\theta]_{315}$ −8480 (negative maximum), $[\theta]_{267}$ −900 (negative minimum) $[\theta]_{253}$ −1050 (negative maximum), $[\theta]_{247}$ 0, $[\theta]_{223}$ +46 500 (positive maximum); ^{1}H NMR data are listed in Table I; mol wt calcd for $C_{19}H_{23}O_6F$: 366.1478, found 366.1499 (by peak matching). Other significant peaks in the high-resolution mass spectrum were at m/z (composition, relative intensity) 296 ($C_{15}H_{17}O_5F$, 0.8), 276 ($C_{15}H_{16}O_5$, 7.9), 258 ($C_{15}H_{14}O_4$, 8.2), 242 ($C_{15}H_{14}O_3$, 19.3), 240 ($C_{15}H_{12}O_3$, 8.4), 230 ($C_{14}H_{14}O_3$, 2.7), 216 ($C_{13}H_{12}O_3$, 7.7), 214 ($C_{14}H_{14}O_2$, 8.1), 213 ($C_{14}H_{13}O_2$, 6.2), 199 ($C_{13}H_{11}O_2$, 7.5), 186 ($C_{13}H_{14}O$, 15.8), 185 ($C_{13}H_{13}O$, 7.6), 73 ($C_3H_5O_2$, 100), 71 (C_5H_{11}, 61.6, and C_4H_7O, 64.9).

(b) Reaction of 50 mg of **5** in 8 mL of dry benzene with 50 mg of $SnCl_4$ overnight at room temperature, dilution with 200 mL of CH_2Cl_2, washing with H_2O, drying, evaporation, and purification of the residue by preparative TLC (benzene–EtOAc, 4:1) gave 25 mg of gummy **2c**: IR 3400 (bonded OH), 1775, 1720 (double strength), 1650, 1260, 1180, 1145 cm^{-1}; CD (EtOH) $[\theta]_{341}$ −732 (sh), $[\theta]_{326}$ −1430 (sh), $[\theta]_{312}$ −1740 (negative maximum), $[\theta]_{280}$ −1030 (negative minimum), $[\theta]_{263}$ −1040 (negative maximum), $[\theta]_{255}$ 0, $[\theta]_{230}$ +55 400 (positive maximum); ^{1}H and ^{13}C NMR spectral data are listed in Tables I and II. Addition of TAI produced no change within 1 h; after 1 week the following signals were observed: δ 8.32 (NH), 3.30 and 2.95 (H-2a,b), 5.50 (H-6), 3.35 (H-7), 5.62 (H-8), 3.26 (H-9b), 2.65 (H-9a), 1.91 (H-14), 2.04 (H-15); mol wt calcd for $C_{19}H_{23}O_6{}^{37}Cl$ and $C_{19}H_{23}O_6{}^{35}Cl$: 384.1154 and 382.1183, found 384.1153 and 382.1190 (by peak matching). Other significant peaks in the high-resolution mass spectrum were at m/z (composition, relative intensity) 346 ($C_{19}H_{22}O_6$), 314/312 ($C_{17}H_{15}O_5Cl$, 9.4 and 31.6), 296/294 ($C_{15}H_{15}O_4Cl$, 9.9 and 33.5), 376 ($C_{15}H_{16}O_5$, 31.5), 260 ($C_{15}H_{16}O_4$, 74.0), 259 ($C_{15}H_{15}O_4$, 33.4), 258 ($C_{15}H_{14}O_4$, 69.0), 248 ($C_{13}H_{12}O_5$, 6.6), 242 ($C_{15}H_{14}O_3$, 65.9), 241 ($C_{15}H_3O_3$, 35.3), 240 ($C_{15}H_{12}O_3$, 56.9), 230 ($C_{14}H_{14}O_3$, 20.1), and 71 (C_5H_{11}, 100).

(c) When the mixture of **5** and $SnCl_4$ in dry benzene was heated on a water bath for 0.5 h, diluted with 200 mL of EtOAc, and worked up as usual, TLC of the crude product showed two spots. The two fractions were separated by preparative TLC (benzene–EtOAc, 4:1). The more polar material was **2c** (15 mg). The less polar material (**8**, 10 mg) was gummy. After some months it showed signs of crystallizing in the NMR tube and was then recrystallized from hexane–ethyl acetate: mp 187–188 °C; IR 1780 (γ-lactone), 1735 (ester), 1720 and 1712 (cyclopentenone and cycloheptanone), 1660, 1655, 1200, 1130, 1075, 1020 cm^{-1}; ^{1}H and ^{13}C NMR spectral data are listed in Tables I and II; significant peaks in the low-resolution mass spectrum at m/z 346, 276, 258, 248, 224, 220, 216, 202, 188, 157, 138, 71; mol wt calcd for $C_{19}H_{22}O_6$: 346.1416, found 346.1419 (by peak matching).

Reaction of 6 with Acids. (a) Epoxide **6** did not react with boron trifluoride etherate at 0–5 °C. When 50 mg of **6** in dry dioxane and diethyl ether was allowed to stand with 10 drops of boron trifluoride etherate at room temperature overnight and worked up in the usual fashion, preparative TLC of the crude residue yielded 30 mg of noncrystalline 1α,10β-dihydroxy-3-oxo-3β-isobutyroxy-4,11(13)guaiadien-6α,12-olide (**9**) which gave a negative periodate test: IR 3450 (bonded OH), 1775, 1715 (double strength), 1655, 1200, 1140, 1075 cm^{-1}; CD (EtOH) $[\theta]_{320}$ −6310 (negative maximum), $[\theta]_{269}$ −930 (sh), $[\theta]_{258}$ 0, $[\theta]_{231}$ +35 200 (positive maximum); ^{1}H and ^{13}C NMR spectral data are listed in Tables I and II. The low- and high-resolution mass spectra did not exhibit the molecular ion; the presence of two hydroxyl groups was shown by the ^{1}H NMR spectrum in the presence of TAI which had the following signals: δ 8.67 and 8.50 (2 NH), 3.26 and 2.95 (H-2a,b), 5.41 (H-6), 3.25 (H-7), 5.78 (H-8), 2.87 (H-9a), 3.35 (H-9b), 6.44 and 5.59 (H-13a,b), 1.73 (H-14), 2.07 (H-15); mol wt − H_2O calcd for $C_{19}H_{24}O_7$ − H_2O: 346.1416, found 346.1417 (by peak matching). Other significant peaks in the high-resolution mass spectrum were at m/z (composition, relative intensity) 276 ($C_{15}H_{16}O_5$, 20.4), 258 ($C_{15}H_{14}O_4$), 242 ($C_{15}H_{14}O_3$, 11.8), 240 ($C_{15}H_{12}O_3$, 8.5), 234 ($C_{13}H_{14}O_4$, 14.5) 233 ($C_{13}H_{13}O_4$, 8.2), 230 ($C_{14}H_{14}O_3$, 3.1), 218 ($C_{12}H_{10}O_4$, 34.0), 216 ($C_{13}H_{12}O_3$, 64.9), 215 ($C_{13}H_{11}O_3$, 51.3), 208 ($C_{15}H_{12}O$, 29.9), 190 ($C_{11}H_{10}O_3$, 41.9), 188 ($C_{12}H_{12}O_2$, 36.6), and 71 (C_4H_7O, 100).

(b) Reaction of 100 mg of **6** in 4 mL of dioxane with 8 drops of $HClO_4$ for 1 h at room temperature, dilution with 200 mL of CH_2Cl_2 followed by the usual workup, and preparative TLC of the crude product gave 70 mg of 1β,10α-dihydroxy-3-oxo-3β-isobutyroxy-4,11(13)-guaiadien-6α,12-olide (**10**) which solidified after some months and was recrystallized from hexane–ethyl acetate: mp 246–248.5 °C; IR 3400 (bonded OH), 1770, 1715 (double strength), 1665, 1650 (sh), 1175, 1140, 1110, 1000, 960 cm^{-1}; CD (EtOH) $[\theta]_{323}$ +8480 (positive maximum), $[\theta]_{280}$ 0, $[\theta]_{243}$ −31 600 (negative maximum), $[\theta]_{231}$ 0, $[\theta]_{219}$ +65 400 (positive maximum); ^{1}H NMR spectral data are listed in Table I. Within 1 h of adding TAI, the mixture showed the signals of a monocarbamate at δ 8.25 (NH), 2.50 and 2.96 (H-2a,b), 5.53 (H-6), 4.09 (H-7), 5.85 (H-8), 2.62 (H-9a), 3.15 (H-9b), 6.32 and 5.63 (H-13), 1.80 (H-14), 2.04 (H-15), 2.36 (H-2′), and 1.05 and 1.13 (H-3′ and H-4′). Weak signals of a dicarbamate were also seen. After 1 week these had increased in intensity and were seen at δ 8.58 and 8.31 (NH); the only signals shifted significantly were those of H-7 at δ 3.67 and H-8 at δ 5.93. H-2a,b and H-9a,b of the dicarbamate were obscured. The low-resolution mass spectrum had significant peaks at m/z 294 ($M^+ - C_4H_6O$), 276 ($M^+ - C_4H_8O_2$), 258, 248, 240, 230, 218, 216, 215, 208, 149, 83, and 71. Peaks at m/z 265 ($M^+ + 1$ by hydrogen transfer) and 364 (M^+) were extremely weak.

1α,10α-Dihydroxy-3-acetoxy-8β-isobutyroxy-11βH-4-guaien-6α,12-olide (16). To a solution of 50 mg of **2a** in 20 mL of MeOH was added with stirring 200 mg of $NaBH_4$ at room temperature. After 10 min the mixture was acidified with acetic acid, diluted with H_2O, and extracted with CH_2Cl_2. The washed and dried extract was evaporated and the residue purified by preparative TLC (benzene–EtOAc, 1:1): yield of gummy **15a** 32 mg; IR 3550, 1775, 1730 cm^{-1}; NMR (270 MHz, $CDCl_3$) δ 5.37 (br t, J = 4 Hz, H-8), 5.15 (br d, J = 9 Hz, H-6), 4.56 (br t, J = 7.5 Hz, H-3), 3.00 (m, H-1), 2.59 (sept, J = 7 Hz, H-2′) 2.51 (dt, J = 15, 7.5 Hz, H-2a), 2.3 (c, H-7, H-9a, H-11), 1.93 (m, H-15), 1.87 (br dd, J = 15, 4 Hz, H-9b), 1.65 (m, H-2b), 1.25 (d, J = 6.5 Hz, H-13), 1.20 (d, J = 7 Hz, H-3′, H-4′); NMR (C_6D_6) δ 5.11 (ddd, J = 4, 3.5, 1 Hz, H-8), 4.95 (dm, J = 11, H-6, also coupled to H-1, H-3, and H-15), 4.17 (br dd, J = 8, 6.5 Hz, H-3, also coupled to H-15 and H-6), 2.47 (br dd, J = 8, 6.5 Hz, H-1, also coupled to H-6 and H-15), 2.23 (dt, J = 14, 8 Hz, H-2a), 2.13 (sept, J = 7 Hz, H-2′), 2.10 (dq, J = 13, 6.5 Hz, H-11), 1.93 (dd, J = 15, 3.5 Hz, H-9a), 1.92 (m, H-15), 1.67 (ddd, J = 13, 11, 1 Hz, H-7), 1.57 (dt, J = 14, 6.5 Hz, H-2b), 1.25 (br dd, J = 15, 4 Hz, H-9b), 1.04 (d, J = 6.5 Hz, H-13), 0.91 (d, J = 7 Hz, H-3′, H-4′), 0.91 (H-14); mass spectrum (low resolution), m/z 352 (M^+), 282, 264, 240, 228. A mixture of **15a** (30 mg) in 2 mL of dry pyridine and 2 mL of Ac_2O was allowed to stand overnight at room temperature. The

usual workup followed by preparative TLC afforded 30 mg of gummy 3-acetoxy-8β-isobutyroxy-10α-hydroxy-11βH-4-guaien-6α,12-olide (**15b**): IR 3600, 1775, 1730, 1720 cm^{-1}; NMR (270 MHz, $CDCl_3$) δ 5.53 (br t, J = 5 Hz, H-3), 5.37 (t, J = 4 Hz, H-8), 5.14 (br d, J = 9.5 Hz, H-6), 3.06 (m, H-1), 2.59 (sept, J = 7 Hz, H-2′), 2.6 (m, H-2a), 2.3 (c, H-7, H-9a, H-11), 2.08 (Ac), 1.9 (m, H-9b), 1.85 (m, H-15), 1.74 (dd, J = 13, 5 Hz, H-2b), 1.26 (d, J = 7 Hz, H-13), 1.21 (d, J = 7 Hz, H-3′, H-4′), 1.14 (H-14); mass spectrum, m/z 334 (M^+), 316, 306, 264, 246, 228; mol wt calcd for $C_{21}H_{30}O_7$: 394.1990, found 394.1975.

A solution of 50 mg of **15b** and 30 mg of SeO_2 in 4 mL of dioxane was refluxed for 4.5 h, diluted with H_2O, and extracted with $CHCl_3$. Evaporation of the washed and dried extract gave a residue which was purified by preparative TLC (benzene–EtOAc, 2:1) to give 32 mg of noncrystalline **16** which gave a positive periodate test: IR 3600, 1775, 1730, 1720 cm^{-1}; NMR (400 MHz) δ 5.50 (t, J = 5 Hz, H-3), 5.33 (t, J = 3.5 Hz, H-8), 5.12 (br d, J = 9.5 Hz, H-6), 2.99 (t, J = 9.5 Hz, H-7 deshielded by C-1 hydroxyl), 2.60 (sept, J = 7 Hz, H-2′), 2.35 (c, H-2a,b, H-9β), 2.26 (m, probably H-11), 2.10 (Ac), 2.03 (dd, J = 15, 3.5 Hz, H-9α), 1.88 (m, H-15); mass spectrum, m/z 410 (M^+), 392, 304, 245; mol wt calcd for $C_{21}H_{30}O_8$: 410.1938, found, 410.1921.

Peracid Oxidation of 2a. (a) A solution of 100 mg of **2a**, 125 mg of *m*-chloroperbenzoic acid, and 20 mg of $SnCl_4$ in 10 mL of CH_2Cl_2 was allowed to stand for 2 weeks at room temperature, diluted with 200 mL of CH_2Cl_2, and worked up as described for the oxidation of **3**. Preparative TLC (benzene–EtOAc, 4:1) of the crude product gave in order of decreasing polarity **17** (20 mg), **19a** (or **20a**, 10 mg), and **18** (10 mg). 2ζ-Chloro-3-oxo-8β-isobutyroxy-10α-hydroxy-1α*H*-4,11(13)-guaiadien-6α,12-olide (**17**) which solidified after several months melted at 219–221.5 °C after recrystallization from hexane–EtOAc: IR 3450 (bonded OH), 1775, 1720, 1715, 1640, 1200, 1140, 1100, 1000, 960, 950 cm^{-1}; ^1H and ^{13}C NMR spectral data are listed in Tables I and II. Addition of TAI resulted in the following shifts: δ 8.35 (NH), 4.09 (H-1), 4.38 (H-2), 5.35 (H-6), 3.50 (H-7), 5.90 (H-8), 2.82 (H-9a), 3.10 (H-9a,b), 6.42 and 5.72 (H-13a,b), 1.46 (H-14); mol wt calcd for $C_{19}H_{23}O_6{}^{37}Cl$ and $C_{19}H_{23}O_6{}^{35}Cl$: 384.1154 and 382.1183, found 384.1154 and 382.1183 (by peak matching). Other significant peaks in the high-resolution mass spectrum were at m/z (composition, relative intensity) 347 ($C_{19}H_{23}O_6$, 1.3), 314/312 ($C_{15}H_{17}O_5Cl$, 0.5 and 2.1) 312 ($C_{15}H_{17}O_5Cl$, 2.1) 296/294 ($C_{15}H_{15}O_4Cl$, 3.8 and 10.8), 295 ($C_{15}H_{16}O_4Cl$, 2.2), 278 ($C_{15}H_{18}O_5$, 1.2), 260 ($C_{15}H_{16}O_4$, 2.5), 259 ($C_{15}H_5O_4$, 6.6), and 258 ($C_{15}H_{14}O_4$, 6.9).

1ζ,11ζ,13-Trichloro-3-oxo-8β-isobutyroxy-10α-hydroxy-1α*H*-4-guaien-6α,12-olide (**18**) remained noncrystalline: IR 3580 (w), 3400 (bonded OH), 1800, 1735, 1728, 1140, 1100, 1000, 950 cm^{-1}; ^1H NMR spectral data are listed in Table I. Addition of TAI produced the following shifts: δ 8.31 (NH), 4.07 (H-1), 4.40 (H-2), 5.73 (H-6), 3.46 (H-7), 5.67 (H-8), 2.75 (H-9a), 3.15 (H-9a,b), 4.19 and 3.19 (H-13a,b), 1.39 (H-14), 2.08 (H-14), 2.08 (H-15). The low-resolution mass spectrum exhibited weak peaks at m/z 456, 454, and 452 in the ratio 0.25, 0.9, and 1, correct for $C_{19}H_{23}O_6{}^{37}Cl_2{}^{35}Cl$, $C_{19}H_{23}O_6{}^{37}Cl{}^{35}Cl_2$, and $C_{19}H_{23}O_6{}^{35}Cl_3$, as well as peaks at m/z 420, 418, and 416 for M^+ – HCl, which did not appear in the high-solution mass spectrum. In the latter, the first significant peaks appeared at m/z 386/384/382 with compositions correct for $C_{15}H_{17}O_5Cl_3$.

Dilactone **19a** or **20a** remained noncrystalline and had IR bands at 1778 (double strength, γ-lactones), 1735 (ester), 1718 (ketone), 1660, 1180, 1140, 1060, 1025, 960, and 925 cm^{-1}; ^1H and ^{13}C NMR spectral data are listed in Tables I and II; mol wt calcd for $C_{19}H_{23}O_7{}^{37}Cl$ and $C_{19}H_{23}O_7{}^{35}Cl$: 400.1103 and 398.1132, found 400.1110 and 398.1135 (by peak matching). Other significant peaks in the high-resolution mass spectrum were at m/z (composition, relative intensity) 358/356 ($C_{17}H_{21}O_6Cl$, 7.2 and 27.7), 330/328 ($C_{15}H_{17}O_6Cl$, 2.9 and 9.8), 297/295 ($C_{15}H_{16}O_4Cl$, 6.1 and 19.6), 288/286 ($C_{13}H_{15}O_5Cl$, 16.4 and 50.7), 276 ($C_{15}H_{16}O_5$, 3.8), 275 ($C_{15}H_{15}O_5$, 13.9), 270/268 ($C_{13}H_{13}O_4Cl$, 15.1 and 44.6).

(b) A solution of 100 mg of **2a**, 125 mg of *m*-chloroperbenzoic acid, and a crystal of *p*-toluenesulfonic acid in 10 mL of CH_2Cl_2 was allowed to stand for 2 weeks at room temperature and worked up as described in the previous section. Preparative TLC (benzene–EtOAc, 1:1) gave 70 mg of starting material in the slower moving band and, in the faster moving band, 20 mg of noncrystalline dilactone mixture: IR 3450, 1775 (double strength), 1730 (br, double strength), 1660 cm^{-1}; mass spectrum, m/z 364 (M^+ of major component), 337 ($M^+ - C_2H_3O$ of minor component), 294, 276, 261, 249, 234, 221, 206, 149, 71. The ^1H NMR spectrum showed that the material was a mixture of two very similar substances, probably **19b** or **20b** (minor component) and **20c** (major component). Signals of the major component appeared at δ 6.38 (d, 4) and 5.72 (d, 3) (H-13a,b), 5.80 (q, 3, H-8) coupled to 3.22 (br d, 10, 3, 3, 3, H-7), 2.53 (dm, 15, H-9a), and 1.98 (dm, 15, H-9b), 5.18 (t, 10, H-6) coupled to H-7, 2.54 (septet, 7, H-2′), 2.41 (H-15), 1.51 (H-14), 1.16 (d) and 1.13 (d) (H-3′ and H-4′). Signals of the minor components were distinguishable at 6.37 (d, 4) and 5.68 (d) (H-13a,b), 5.80 (q, 3, H-8), coupled to 3.41 (br d, 10, H-7), which was in turn coupled to 5.28 (d, 10, H-6), 2.37 (H-15), 2.01 (dm, H-9b), and 1.50 (H-14). The other signals were identical with those of the major component.

X-ray Analysis of 8. Single crystal of **8**, prepared by slow crystallization from benzene–ethyl acetate, were monoclinic, space group $P2_1$, with a = 8.829 (3) Å, b = 6.694 (3) Å, c = 16.166 (5) Å, β = 104.70 (2)°, and d_{calcd} = 1.245 g cm^{-3} for Z = 2 ($C_{19}H_{22}O_6$, M_r = 346.38). The intensity data were measured on a Hilger-Watts diffractometer (Ni-filtered Cu Kα radiation, θ–2θ scans, pulse-height discrimination). The size of the crystal used for data collection was approximately 0.2 × 0.6 × 1.2 mm. A total of 1197 accessible reflections were measured for θ < 57°, of which 1169 were considered to be observed [$I > 2.5\sigma(I)$]. The structure was solved by a multiple-solution procedure[34] and was refined by full-matrix least-squares methods. Preliminary anisotropic refinement indicated that C-22 and C-23 were disordered. Each of these atoms were replaced by two carbon atoms of half-weight to account for the disorder. In the final refinement, anisotropic thermal parameters were used for the nonhydrogen 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 = 0.060 and R_w = 0.078 for the 1169 observed reflections. The final difference map has no peaks greater than ±0.3 e $Å^{-3}$.

Registry No. 1, 59979-56-5; **2a**, 75197-71-6; **2b**, 84558-14-5; **2c**, 84537-37-1; **2d**, 84537-38-2; **3**, 75197-72-7; **4a**, 1618-98-0; **4b**, 7759-23-1; **5**, 84537-39-3; **6**, 84620-28-0; **8**, 84537-40-6; **9**, 84537-41-7; **10**, 84537-42-8; **15a**, 84537-43-9; **15b**, 84537-44-0; **16**, 84537-45-1; **17**, 84537-46-2; **18**, 84537-47-3; **19a**, 84537-48-4; **19b**, 84537-49-5; **20a**, 84537-50-8; **20b**, 84537-51-9; **20c**, 84537-52-0.

Supplementary Material Available: Table II listing ^{13}C NMR spectra of compounds **2a,c**, **5**, **6**, **8**, **9**, **17**, and **19a** and Tables III-VI listing final atomic parameters, final anisotropic thermal parameters, bond lengths, and bond angles for compound **8** (6 pages). Ordering information is given on any current masthead page.

(32) Compare with $J_{7,11}$ = 11.5 Hz in acetylphotosantonic acid lactone.
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(34) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* **1971**, *A27*, 368.