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BIOMIMETIC TRANSFORMATIONS OF 11,13-DIHYDROPARTHENOLIDE AND OXIDATIVE REARRANGEMENTS OF A GUAI-1(10)-EN-6,12-OLIDE

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ABSTRACT.—A reinvestigation of BF_3-mediated rearrangement products of 11,13-dihydroparthenolide [**1**] provided, besides the previously obtained dihydromichelliolide [**5**], the following new products: the xanthanolide 2-desoxy-11β,13-dihydro-epiparthemollin [**2**], a 4-methylene-5α-hydroxy-*cis*-guaianolide [**3**], and the *cis*-guaianolide compressanolide [**4**]. Their mechanisms of formation were interpreted as rearrangements involving carbocation intermediates.

Peracid oxidation of guaianolide **5** in CH_2Cl_2 produced the guaianolide-1(10)-β-epoxide [**9**] as the major product and the 1(10)-α-epoxide **8** as a minor component. In addition, the epoxyguaianolide [**6**], its presumed rearranged cyclobutane-type lactone **7**, and the xanthanolide **10** were found as minor reaction products. The structure elucidations of the new compounds were performed by spectral methods, and the molecular structures of epoxides **6** and **8** were determined by single crystal X-ray diffraction.

Due to the lack of biosynthetic data, in vitro transformations of sesquiterpene lactones have in the past provided indirect evidence for their possible biosynthetic pathways. A series of biomimetic interconversions of different skeletal types of sesquiterpene lactones were previously reported (1–10). A biogenetic hypothesis proposes that germacrolides and their epoxide derivatives represent the precursors for other skeletal types of sesquiterpene lactones (10–13). For instance, Lewis-acid-catalyzed reactions of germacra-1(10),4(5)-dienolides as well as their 1(10)-epoxide derivatives favor formation of *trans*-decalin-type eudesmanolides (14–18). In vitro cyclizations of germacrolide-4-epoxides into guaianolides (19–21) and xanthanolides (22,23)[1] and the transformation of a guaianolide into a pseudoguaianolide (24)[2] strongly suggest the involvement of cyclodeca-1,5-diene derivatives in the biosynthesis of other skeletal types of sesquiterpene lactones. This is in analogy to the non-lactonic sesquiterpene biosynthetic hypothesis, which is based on relationships derived from their biomimetic transformations (25–31).

This present study represents a reinvestigation of previously performed BF_3-mediated cyclization experiments of 11,13-dihydroparthenolide [**1**], with major emphasis on the isolation and structure determination of previously unidentified minor cyclization products (1). Besides the known major guaianolide **5** (1,19), two further guaianolides **3** and **4** and a xanthanolide **2** were obtained.

The peracid-oxidation of lactone **5** gave guaianolide 1(10)-β-epoxide [**9**] as the major product, and the cyclobutane-type sesquiterpene lactone **7**, epoxyguaianolides **6** and **8**, and xanthanolide **10** were formed as minor products. The structure determinations of the newly obtained cyclization and rearrangement products and their mechanism of formation are discussed below.

RESULTS AND DISCUSSION

BF_3-INITIATED CYCLIZATIONS OF 11,13-DIHYDROPARTHENOLIDE [**1**].—The structure of 11,13-dihydroparthenolide [**1**] was previously determined by low-field

[1]In our communication on the formation of xanthanolide **2** from 11,13-dihydroparthenolide [**1**] (23) we failed to acknowledge the first report by Wilton and Doskotch on a transformation of a germacrolide into a xanthanolide (22). We very much regret this serious oversight.

[2]The first cyclization of a germacranolide-4-epoxide into a pseudoguaianolide was reported by A. Ortega at the First Latinamerican Congress of Phytochemistry, Mexico City, Mexico, March 3–6, 1986.

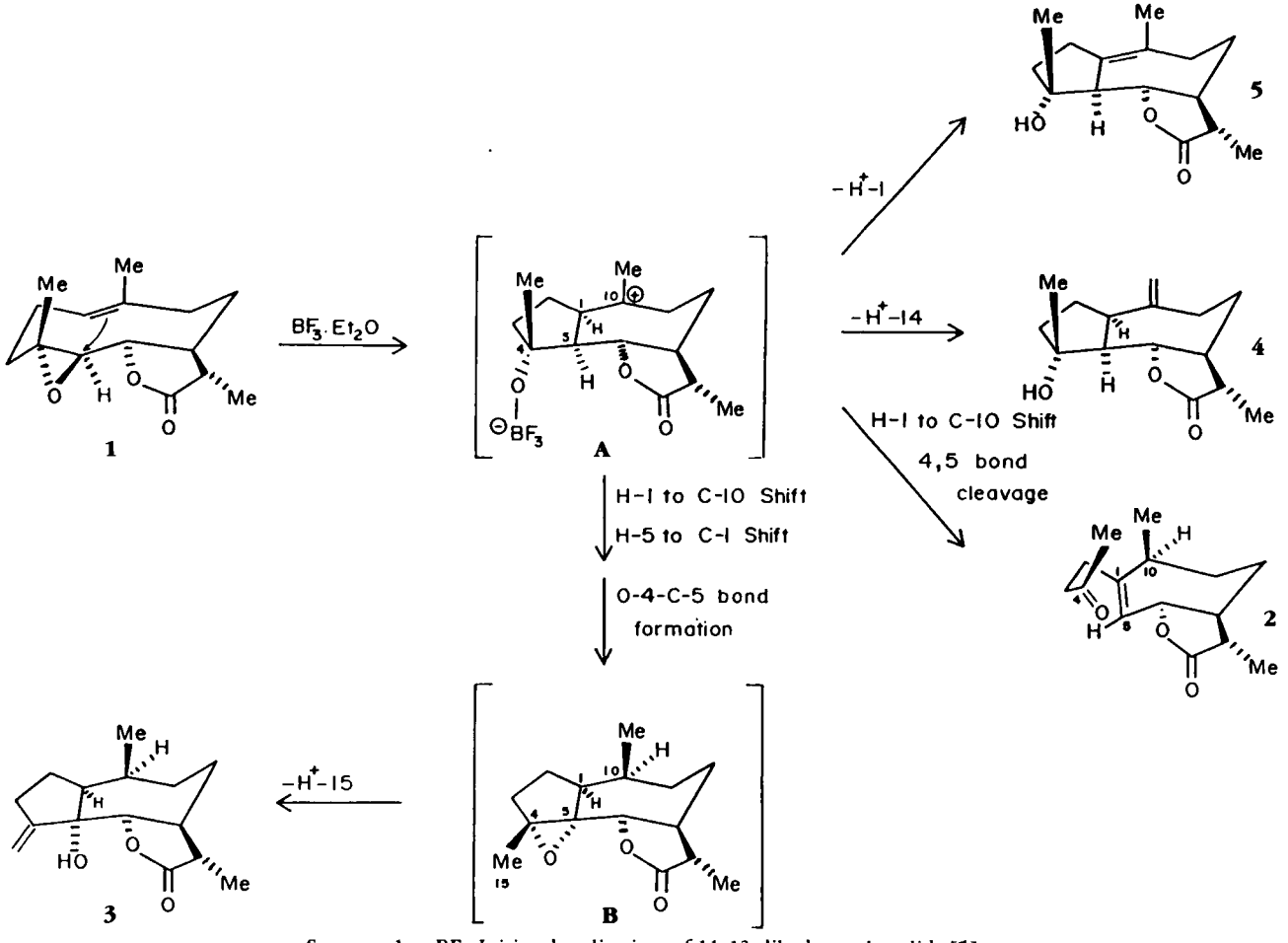
nmr data and degradation experiments (19). Because previous data were incomplete, the present study includes high-field nmr spectral data of lactone **1**. The germacrolide **1** was used as a model to established its molecular framework by 2D $^{13}C^{13}C$ shift spectral correlation (32). ^{1}H-nmr assignments were also obtained from 2D ^{1}H ^{13}C correlation, COSY spectra, and analysis of coupling constants, as well as data provided by nOe difference spectroscopy experiments (33,34). The solute conformation of **1** indicated that the methyl groups at C-4 and C-10 are β-oriented and the 1(10) double bond and the 4(5)-epoxide are trans and crossed, as in the conformation of parthenolide which had been established by X-ray analysis (35).

Xanthanolide **2** had strong ir absorption bands at 1715 (ketone) and 1779 cm^{-1} (γ-lactone). The cims exhibited a base peak at *m/z* 251 $[M+H]^+$, and the eims showed major peaks at *m/z* 232 $[M-H_2O]^+$, 208 $[M-C_2H_2O]^+$, and 192 $[M-C_3H_6O]^+$. The latter two fragments, together with a methyl singlet at δ 2.2 and a ^{13}C-nmr signal at δ 29.9, supported the presence of a methyl ketone moiety. A 2D homonuclear correlation ^{1}H-nmr spectrum of **2** showed a deshielded lactonic proton at δ 4.8 ppm (H-6) with a small coupling to a broad singlet at δ 5.6 assigned to an olefinic proton (H-5). The sequence of coupled protons (H-5 to H-10) was disrupted at the allylic proton H-10, the latter proton being α-oriented and geminal to a methyl doublet that exhibited a positive nOe with the allylic lactonic proton (H-6). This indicated a major conformation in **2** that places the lactonic proton almost perpendicular to H-5 and in close proximity to 10-Me.

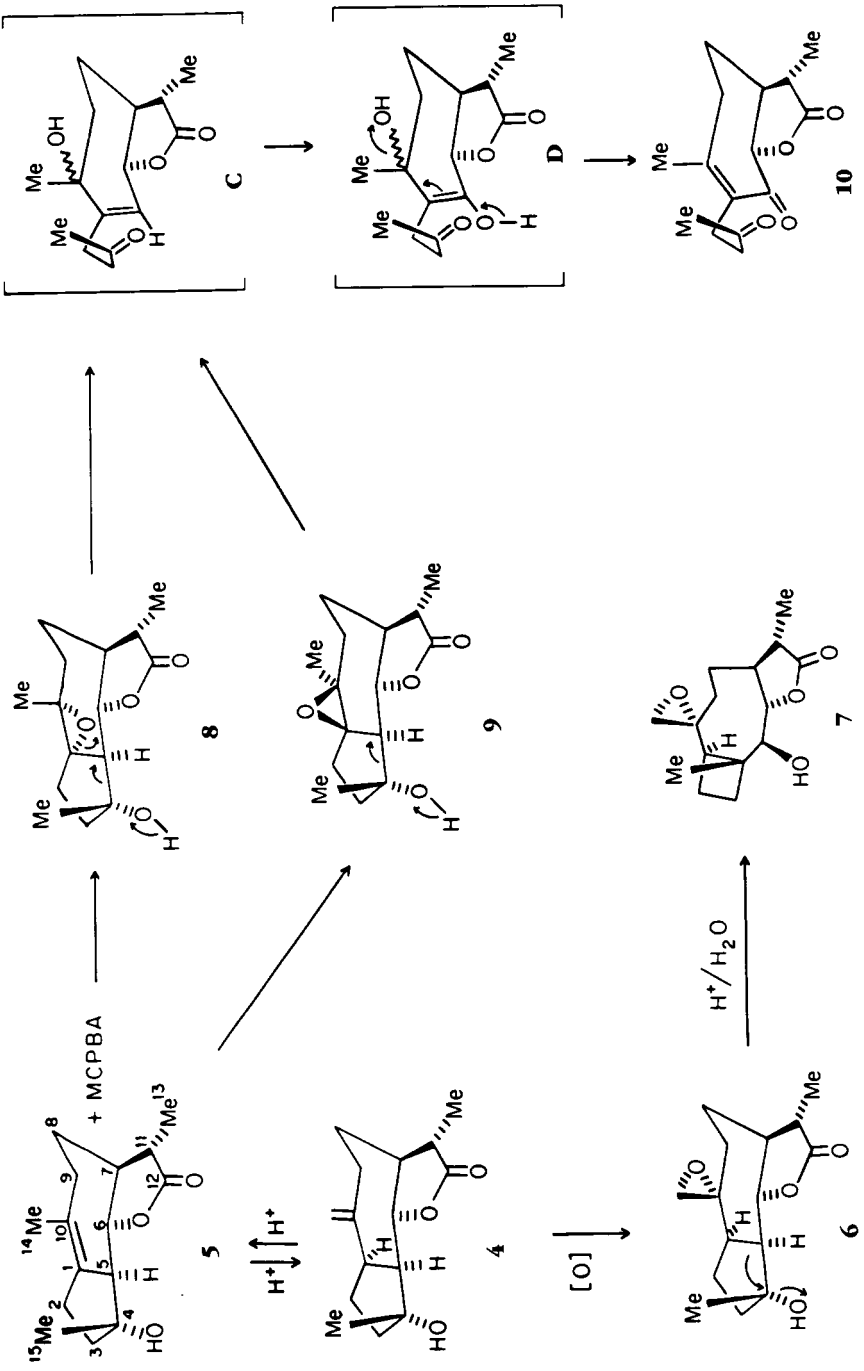
The structure determination of guaianolides **4** and **5** involved comparison of their spectroscopic data with those of known compounds previously reported in the literature (4,17). The trichloroacetylcarbamate derivative of **5** exhibited paramagnetic shift of 0.5 for H-5 and 0.35 ppm for the 4-Me. This supported previous findings (17) that the hydroxyl geminal to the C-4 methyl group is α-oriented. Furthermore, irradiation of 4-Me signals resulted in a positive nOe of the lactonic proton (H-6) and no nOe at H-5, indicating the relative configuration of C-4, C-5, and C-6 as shown in structures **4** and **5**. A positive nOe between H-1 and H-5 supported a *cis*-guaianolide-type structure for lactone **4**.

Inspection of the ^{1}H-nmr spectrum of guaianolide **3** indicated that no proton was present at C-5 since H-6 appeared as a doublet at δ 3.88. In addition, the spectrum lacked an absorption for the 4-Me geminal to the hydroxyl as in **4** and **5**. Instead, olefinic exocyclic protons at δ 5.0 and δ 5.08, as well as an oxygen-bearing allylic quaternary carbon (C-5, δ 86.5), were observed, suggesting a 4-methylene-5α-hydroxy-*cis*-guaianolide, as presented by structure **3**. Assignment of an α configuration of the C-5 hydroxyl group in **3** was based on mechanistic grounds (Scheme 1) as well as ^{1}H-nmr spectral data. Guaianolides with a 5β-oxygen function cause a distinct downfield shift of the lactonic H-6β to near 5 ppm (36). Because in **3** H-6 appeared at 3.88 ppm, a β configuration of the C-5 hydroxyl group was excluded.

Scheme 1 outlines the BF_3-initiated carbocationic transannular cyclization of 11,13-dihydroparthenolide and summarizes the sequences of steps leading to the isolated reaction products **2–5**. From its chair-like transition state conformation **1**, the *cis*-fused guaianolide cation **A** is generated which by loss of a proton from C-14 or C-1 forms the guaianolides **4** and **5**, respectively. Alternatively, shift of C-1α hydrogen in **A** to the cationic center C-10 could initiate a fragmentation of the C-4–C-5 bond to form the xanthanolide **2**. From intermediate **A**, H-1 to C-10α hydride shift followed by a C-5α to C-1α hydride shift could lead to a 4(5)-epoxide intermediate **B** which can undergo eliminative opening of the highly strained epoxide to give the *cis*-guaianolide **3**. In Table 1 the gas-liquid chromatographic retention times on OV-1 and DB-17 liquid phase columns of lactones **1–5** are tabulated.



SCHEME 1. BF_3-Initiated cyclizations of 11,13-dihydroparthenolide [**1**].



SCHEME 2. Peracid-mediated oxidative rearrangements of guaianolide **5**.

TABLE 1. Gas-Liquid Chromatographic Retention Times (Rt) of Lactones **1–5**.[a]

	Compound				
	1	**2**	**3**	**4**	**5**
Rt[b]	13.75	11.73	10.85	10.75	10.93
Rt[c]	26.88	23.17	22.08	22.17	21.65

[a]Temperature program: 130°/1 min, 5°/min, 260°/3 min. 10 psig column pressure (He). Injector temperature 275°, transfer zones 250°, source temperature 200°. Retention times (Rt) are in min.

[b]20 m × 0.25 mm × 0.2 μm OV-1 BP.

[c]30 m × 0.25 mm × 0.25 μm film DB-17.

PERACID OXIDATION OF THE GUAIAN-1(10)-EN-6,12-OLIDE [**5**].—Scheme 2 outlines the peroxyacid-mediated oxidation rearrangement of the guaianolide **5**. Epoxidation of the 1(10)-double bond of guaianolide **5** with *m*-chloroperbenzoic acid (mcpba) proceeded preferentially from the less hindered β side of the lactone affording as a major product the guaianolide 1(10)-β-epoxide [**9**] and α-epoxide **8** as a minor reaction product.

Guaianolide-1(10)-epoxides **8** and **9** presented similar mass spectral fragmentations with major peaks at *m/z* 266 $[M]^+$, 233 $[M - H_2O - Me]^+$, 223 $[M - MeCO]^+$, 208 $[M - C_3H_6O]^+$, and 97 $[C_6H_9O]^+$. 2D ^{1}H-nmr COSY spectra of **8** and **9** established the relationships between the series of protons, and their 2D ^{1}H ^{13}C correlated nmr spectra showed the connectivities between carbons and directly attached protons (Tables 2 and 3). The assignments of ^{13}C-nmr resonances of **8** were derived from 2D heteronuclear relayed correlation experiment (37). The molecular structure of **8** was confirmed by single crystal X-ray diffraction and will be discussed later. Details of the structure of β-epoxide **9** (1) including its molecular structure are described elsewhere (38).

Although ^{1}H nmr chemical shifts for H-5, H-6, and H-8β for epoxides **8** and **9** were similar, differences in the stereochemistry of the two epoxides were indicated by the following spectral data: (a) a clear nOe was observed for H-6 upon irradiation of H-8β in **8** but not in **9**; (b) a positive nOe was shown for H-9β and H-2α upon irradiation of 10-Me in **8**; and (c) a significant paramagnetic shift ($\Delta\delta = 0.45$ ppm) was observed for H-7 in **8**. This strong deshielding effect of the epoxide group upon H-7α in **8** strongly suggested that **8** represents the α-epoxide isomer of **9** (38). This was further confirmed by the X-ray data of compounds **8** and **9** (38).

The ir spectrum of the *cis*-guaianolide **6** showed absorptions for hydroxyl at ν 3509 cm^{-1} and a γ-lactone at ν 1773 cm^{-1}. Mass spectral peaks at *m/z* 251 $[M - Me]^+$, 248 $[M - H_2O]^+$, 233 $[M - Me - H_2O]^+$, and 208 $[M - C_3H_6O]^+$ indicated fragmentations similar to those observed for its guaianolide precursor **4**. 2D-nmr heteronuclear correlation of protons at δ 2.55 and 2.78 with the ^{13}C-nmr resonance at δ 47.9 and comparison of the resonances of oxygenated quaternary carbons C-4 (δ 79.6) with analogous carbons of **9** (δ 79.6) and **8** (δ 79.8), as well as C-10 (δ 58.0) with C-10 of **7** (δ 57.4), indicated the presence of an exocyclic 10(14)-epoxide and methyl geminal to hydroxyl at C-4. The COSY spectrum suggested disruption of an extended sequence of coupled protons at quaternary carbons C-4 and C-10. Positive nOe's between H-1 and H-5 and between 4-Me and H-14a as well as H-6 allowed determination of the relative configuration of the chiral centers at carbons 1,4,5,6, and 10 as shown in the stereoformula for 10(14)-epoxyguaianolide **6**. The above spectral assignments were confirmed

TABLE 2. ^{13}C-nmr Spectral Data of Sesquiterpene Lactones **1–10**.[a]

Carbon	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
C-1	125.0 d	145.7 s	43.6 q	44.1 d	132.0 s	42.2 d	43.1 (43.0) d	70.3 s	69.8 (70.2) s	135.8 s
C-2	24.0 t	33.2 t	31.1 t	32.9 t	35.2 t	28.7 t	17.7 (17.8) t	29.0 t	29.4 (29.8) t	34.4 t[b]
C-3	36.6 t	41.7 t	35.2 t	39.5 t[b]	38.4 t	38.8 t	30.7 (31.1) t	37.0 t	37.4 (38.5) t	40.4 t
C-4	61.3 s	207.7 s	144.4 s	79.8 s	80.2 s	79.6 s	43.0 (43.0) s	80.6 s	79.6 (79.7) s	207.1 s
C-5	66.3 d	123.8 d	86.5 s	55.7 d	58.2 d	54.7 d	85.5 (85.1) d	59.5 d	55.2 (55.4) d	176.5 s
C-6	82.0 d	81.0 d	78.8 d	83.9 d	84.0 d	83.4 d	83.4 (83.0) d	79.7 d	81.6 (81.8) d	76.3 d
C-7	51.8 d	51.0 d	48.3 d	51.6 d	53.5 d	50.8 d	48.0 (47.5) d	50.9 d	53.1 (53.4) d	46.3 d
C-8	29.7 t	31.4 t	26.9 t	26.3 t	27.0 t	25.7 t	26.6 (26.3) t	23.9 t	23.1 (23.7) t	25.4 t
C-9	41.0 t	25.3 t	25.4 d	40.2 t[b]	29.9 t	39.1 t	39.4 (39.6) t	34.0 t	33.4 (33.7) t	32.4 t[b]
C-10	134.4 s	37.4 d	41.6 d	148.7 s	131.0 s	58.0 s	57.4 (56.9) s	63.0 s	62.1 (62.4) s	—
C-11	42.3 d	42.3 d	41.9 d	41.4 d	41.1 d	41.2 d	44.2 (43.9) d	42.0 d	40.7 (40.7) d	41.7 d
C-12	177.2 s	178.7 s	178.0 s	178.2 s	178.2 s	—	176.5 (175.8) s	177.8 s	178.0 (178.2) s	178.3 s
C-13	13.1 q	12.4 q	12.6 q	13.2 q	12.2 q	13.1 q	12.9 (12.8) q	12.6 q	12.4 (12.4) q	14.6 q
C-14	16.7 q	15.8 q	18.9 q	112.0 t	23.6 q[b]	47.9 t	51.4 (51.0) t	24.3 q	23.2 (23.3) q[b]	17.8 q
C-15	17.0 q	29.9 q	114.7 t	24.1 q	23.7 q[b]	23.9 q	16.2 (16.2) q	21.8 q	23.2 (23.2) q[b]	29.9 q

[a]Spectra were obtained in $CDCl_3$ at 50 MHz for **2–5** and 100 MHz for **1**, **6–10**; data in parentheses were obtained in C_6H_6 for **7** and Me_2CO-d_6 for **9**. Assignments of compounds **1–10** are based on DEPT (33) and $^1H^{13}C$ correlation experiments for lactones **6–9**.

[b]Interchangeable assignments.

TABLE 3. ^{1}H-nmr Spectral Data[a] of Sesquiterpene Lactones **6–10** at 400 MHz.[b]

Proton	6[c]	7[d]	8[c]	9[c]	10[e]
H-1	2.95 ddd	2.10 dd (2.62)	—	—	—
H-2α	1.30	1.62 (1.72)	2.09	2.21	2.41
H-2β	2.09	1.34 (1.57)	1.80	1.66	2.60
H-3α	1.96 ddd	1.70 (1.90)	2.01	1.90	2.60
H-3β	1.57 ddd	1.47 (1.60)	1.80	1.85	2.41
H-5	2.30 dd	2.97 d (3.61)	2.23 dd	2.24 d	—
H-6	4.12 dd	3.46 dd (4.08)	3.98 dd	4.06 dd	4.80 d (4.55)
H-7	1.82	1.12 (1.80)	1.83	1.38	2.48
H-8α	1.70	1.08 (1.86)	2.00	1.68	1.72
H-8β	0.98	0.87 (1.70)	1.37	1.35	1.80
H-9α	1.71	1.40 (1.88)	2.20	1.92	2.45
H-9β	1.81	1.08 (1.50)	1.68	2.16	2.45
H-11	2.28 dq	1.53 dq (2.30)	2.18	2.20	2.35
H-13	1.22 d	0.92 d (1.24)	1.21 d	1.20 d	1.34 d (1.15)
H-14	2.78 d	2.61 dd (3.03)	1.43 s	1.46 s	2.18 br s (1.52)
	2.55	2.12 d (2.62)			
H-15	1.26	0.91 s (1.21)	1.27 s	1.29 s	2.10 s (1.58)

[a]Compound **9**: $J_{5,6}=J_{6,5}=11.0$, $J_{6,7}=9.8$, $J_{13,11}=7.0$. Compound **7**: $J_{5,6}=J_{6,5}=9.3$, $J_{6,7}=10.3$, $J_{11,7}=12.1$, $J_{11,13}=J_{13,11}=7.0$, $J_{14a,14b}=J_{14b,14a}=4.4$. Compound **8**: $J_{5,6}=J_{6,5}=11.2$, $J_{6,7}=10.3$, $J_{13,11}=7.2$. Compound **6**: $J_{1,2\alpha}=10.5$, $J_{1,2\beta}=10.0$, $J_{1,5}=J_{5,1}=11.8$, $J_{3\alpha,2a}=10$, $J_{3\alpha,2\beta}=2.0$, $J_{3\alpha,3\beta}=J_{3\beta,3\alpha}=12.0$, $J_{5,6}=J_{6,5}=11.3$, $J_{6,7}=10$, $J_{11,7}=12.1$, $J_{11,13}=J_{13,11}=6.9$, $J_{14a,14b}=4.0$. Compound **10**: $J_{6,7}=9.3$, $J_{13,11}=6.8$. NOe's irradiated (observed): Compound **9**, 8β,15 (6); Compound **7**, 1 (2α,5), 5 (1), 6 (11), 7 (5,9α), 9α (7), 14a (14b), 14b (14a), 15 (6,14a); Compound **6**, 1 (2α,5), 5 (1), 6 (11), 7 (5,9α), 9α (7), 14a (14b), 14b (14a), 15 (6,14a); Compound **10**, 6 (11), 8 (6), 14 (2b).

[b]Assignments of **6**, **8**, and **9** were based on 2D COSY and ^{1}H ^{13}C correlation spectra. COSY spectrum of **10** was obtained.

[c]In $CDCl_3$.

[d]In C_6D_6 ($CDCl_3$).

[e]In $CDCl_3$ (C_6D_6).

by determination of the molecular structure using single crystal X-ray diffraction. These data will be discussed at the end of this paper.

As outlined in Scheme 2, formation of **6** could proceed under acidic reaction conditions via acid-mediated pre-equilibration of guaianolide **5** with its *exo*-double bond isomer **4** followed by epoxidation from the less hindered α side of the 10(14)-double bond of **4**. Protonation of the C-4 hydroxyl group in **6** and loss of H_2O could initiate rearrangement of the C-1–C-5 bond to form a C-1–C-4 bond. Nucleophilic attack of H_2O at the cationic center C-5 would give cyclobutane-type lactone **7**.

The cims of **7** exhibited a base peak at *m/z* 267 $[M+H]^+$ and strong ir absorption for hydroxyl at ν 3459 cm^{-1}. The COSY spectrum of **7** indicated that C-4 and C-10 had to be quaternary carbons, one of which had a ^{13}C-nmr resonance at δ 57.4 indicating an oxygenated carbon. The other quaternary carbon with a signal at δ 43.0 was part of a cyclobutane ring as established by comparison of the ^{13}C-nmr resonances, which were obtained by heteronuclear correlation with the smallest series of coupled protons provided by COSY with those of a similar four-membered ring lactone (22). In addition to the long-range coupling between the oxygenated methylene protons H-14a at δ 2.61 (^{13}C nmr δ 51.4) and H-9β, nOe's between H-8β and H-6 and between H-15 and H-14a as well as H-6, and nOe between H-1 and the proton at oxygen-bearing C-5 (δ 85.5) allowed assignments of the stereochemistry of **7**.

The hydroxyl group at C-5 had to be β-oriented, and the cyclobutane had to be *trans*-fused with an 8-membered ring. Formation of the four-membered ring in **7** could

involve rearrangement of the C-1–C-5 bond of **6** to form the C-1–C-4 bond. This rearrangement might be induced by acid-mediated carbocation formation at C-5.

The cims of xanthanolide **10** exhibited a base peak at *m/z* 265 $[M + H]^+$, and the eims showed major peaks at *m/z* 221 $[M - MeCO]^+$ and 206 $[M - C_3H_6O]^+$. The latter two ms fragments together with an ir absorption at ν 1715 cm^{-1}, a three-proton ^{1}H-nmr signal at δ 2.12, and a ^{13}C-nmr resonance at 217 ppm supported a methyl ketone moiety. Evidence for the presence of an additional α,β-unsaturated carbonyl system was provided by an ir absorption at ν 1701 cm^{-1}, ^{13}C nmr resonances at δ 176.5 and δ 135.8 (α- and β-carbons of an α,β-unsaturated ketone), and a three-proton signal at δ 2.18, indicating a methyl at a β-carbon. A significant deshielding of the doublet for the lactonic proton (H-6, δ 4.8) strongly suggested the ketone moiety at C-5 and an overall structure as shown in formula **10**.

Formation of the xanthanolide **10** could involve either of the guaianolide 1(10)-epoxides **8** or **9**. Cleavage of the C-1-oxygen bond in **8** or **9** could initiate fragmentation of the C-4–C-5 bond to form a xanthanolide intermediate **C**. Epoxidation of the 4,5 double bond followed by acid-mediated epoxide rearrangement under enol formation would lead to enol **D**. Subsequent acid-mediated elimination of the C-10 hydroxyl group would generate the α,β-unsaturated ketone group in compound **10**.

CRYSTAL STRUCTURE ANALYSIS OF LACTONES **6** AND **8**.—The molecular structure of *exo*-epoxide **6** is illustrated in Figure 1, which shows the epoxy group to be in the α configuration, with C-14 oriented axially. Bond distances are normal, and the precision of the determination is high, with standard deviations in the bond lengths typically 0.001 Å. The epoxide is slightly asymmetric, with C-14–O-3, 1.439(2) Å, slightly shorter than C-10–O-3, 1.451(1) Å. The seven-membered ring is in the chair conformation, with pseudomirror passing through C-8 and bisecting the C-1–C-5 bond. The lactone ring is in the envelope conformation with C-7 at the flap. The other five-membered ring is in a conformation intermediate between envelope with C-3 at the flap and half chair with C-1 on the pseudo-twofold axis. Molecules are linked in the solid by weak hydrogen bonds involving the OH group and the lactone carbonyl oxygen atom, O . . . O distance 2.993(2) Å and angle at H 150(2)°.

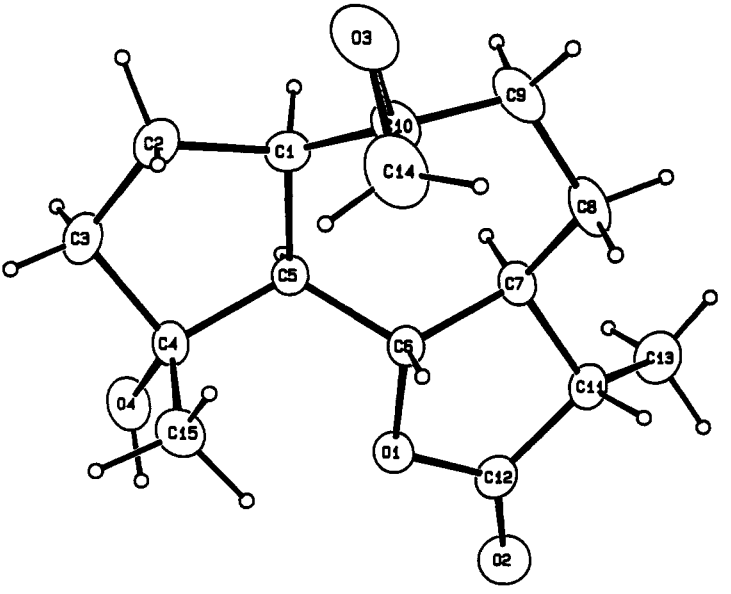


FIGURE 1. Molecular Structure of **6**.

The molecular structure of 1(10)-epoxide **8** is illustrated in Figure 2, which shows the epoxy group to be α-oriented. Bond distances agree well with those of **6**, except for those expected to be different because of the different location of the epoxide. The precision is slightly lower, with typical standard deviations in bond distances 0.003 Å. The epoxide is slightly asymmetric with O-3–C-1, 1.449(2) Å, slightly shorter than O-3–C-10, 1.464(2) Å. The seven-membered ring is in the chair conformation with C-7 on the pseudomirror, unlike **6**, in which C-8 occupies that position. The epoxy function apparently imposes this conformation by restricting the endocyclic torsion angle about C-1–C-10 to be near zero. As in **6**, the lactone ring is in the envelope conformation with C-7 at the flap and is somewhat more puckered. The average endocyclic torsion angle magnitude for this ring in **8** is 25.1°, as compared to 18.3° in **6**. The cyclopentane ring of **8** is in an intermediate conformation between the envelope with C-4 at the flap and the half-chair with C-2 on the pseudo-twofold axis. This ring is only slightly more puckered than that of **6**, with mean endocyclic torsion angle magnitudes respectively 28.1° and 25.9°.

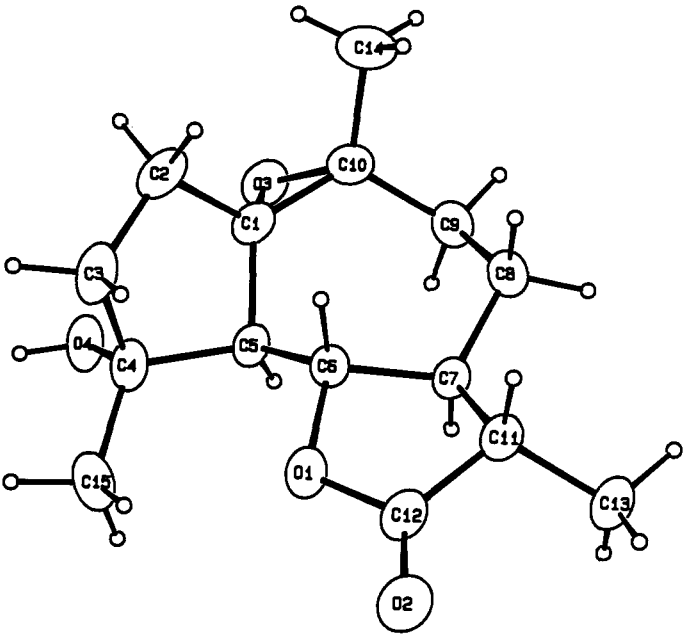


FIGURE 2. Molecular Structure of **8**.

The function of the H_2O molecule in the solid-state structure of **8** is to form hydrogen-bonded links between molecules. The H_2O molecule donates near-linear hydrogen bonds to lactone carbonyl O-2 [2.928(3) Å] and hydroxy group O-4 [2.866(3) Å]. The hydroxy group is also involved in another intermolecular hydrogen bond to the epoxy oxygen with O-4 . . . O-3 distance 2.884(2) Å and angle at H 169(3)°.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined on a Thomas Hoover apparatus and are uncorrected. Spectra were recorded on the following instruments: nmr, Bruker AM 400 (400 MHz), Bruker WP 200 (200 MHz); ir, IBM-32; ms, HP-5985 gc-ms-ds. 11,13-Dihydroparthenolide [**1**] was isolated from local common ragweed, *Ambrosia artemisiifolia* L. (Compositae), by a previously described method (1).

BF_3-CATALYZED REARRANGEMENT OF 11,12-DIHYDROPARTHENOLIDE [**1**].—A solution of **1** (1 g) in 100 ml of dry Et_2O was treated with 10 ml of freshly distilled BF_3-etherate, (39,40) left at room tem-

perature for 2.5 h and worked up as described in the literature (19). The crude gummy product was chromatographed over Si gel using $CHCl_3$ and increasing the polarity with Me_2CO yielding, in order of appearance, crude **2–5**. Rechromatography by preparative tlc over Si gel using CH_2Cl_2-Et_2O (2:1) provided pure **2** (20 mg); with CH_2Cl_2-Et_2O (1:1) lactone **3** (10 mg) was obtained, and using CH_2Cl_2-Et_2O (5:1) provided **4** (30 mg). Recrystallization of the late fractions in $CHCl_3$ gave pure **5** (470 mg). The remaining fractions (210 mg) consisted of a mixture (1:8:1) of **1**, **5**, and a complex isomeric mixture that was not possible to separate.

11,13-Dihydroparthenolide [**1**].—Compound **1**: $C_{15}H_{22}O_3$, mol wt 250, colorless crystals, mp 134–136° [lit. (1) mp 137–137.5°]; eims *m/z* (% rel. int.) $[M]^+$ 250 (5.2), $[M-Me]^+$ 235 (7.9), $[M-H_2O]^+$ 232 (8.3), $[M-Me-H_2O]^+$ 217 (5.3), $[M-MeCO]^+$ 207 (50.8), $[C_4H_7]^+$ 55 (68.9), $[MeCO]^+$ 43 (40.4), $[C_3H_5]^+$ 41 (20.8); ^{1}H nmr (400 MHz) δ 5.17 (dd, H-1), 2.07 (H-2α), 2.32 (H-2β), 1.17 (H-3α), 2.05 (H-3β), 2.68 (d, H-5), δ 3.80 (dd, H-6), 1.86 (H-7), 1.83 (H-8α), 1.63 (H-8β), 1.99 (H-9α), 2.22 (H-9β), 2.27 (H-11), 1.21 (d, 3H, H-13), 1.63 (br s, 3H, H-14), 1.24 (s, 3H, H-15); $J_{1,2\alpha}=2$, $J_{1,2\beta}=J_{2\beta,1}=11$, $J_{2\beta,2\alpha}=12.4$, $J_{3\alpha,3\beta}=13.1$, $J_{3\alpha,2\beta}=12.9$, $J_{3\alpha,2\alpha}=5.9$, $J_{5,6}=J_{6,5}=9.0$, $J_{6,7}=9.4$, $J_{13,11}=7.1$; ir ν max (neat) 1771 (γ-lactone), 1673 (C=C) cm^{-1}.

2-Desoxy-11β,13-dihydro-6-epi-parthemollin [**2**].—Compound **2**: $C_{15}H_{22}O_3$, mol wt 250, gum; eims *m/z* (% rel. int.) $[M-Me]^+$ 235 (0.4), $[M-H_2O]^+$ 232 (2.6), $[M-C_2H_2O]^+$ 208 (6.5), $[M-C_3H_6O]^+$ 192 (42.1), $[C_9H_{11}]^+$ 119 (14.4), $[C_4H_7]^+$ 55 (47.0), $[MeCO]^+$ 43 (100.0); NH_3 cims $[M+NH_4]^+$ 268, $[M+H]^+$ 251, $[M+H-H_2O]^+$ 233; ^{1}H-nmr (200 MHz) δ 2.3 (H-2a), 2.3 (H-2b), 2.6 (H-3a), 2.6 (H-3b), δ 5.6 (br s, H-5), 4.8 (br d, H-6), 1.6 (H-7), 1.6 (H-8a), 1.6 (H-8b), 1.9 (H-9a), 1.9 (H-9b), 2.3 (H-11), 1.2 (d, 3H, H-13), 1.1 (d, 3H, H-14), 2.2 (s, 3H, H-15); $J_{14,10}=J_{11,13}=J_{5,6}=J_{6,5}=7.0$ (COSY experiment was carried out at 200 MHz); ir ν max (neat) 1715 (C=O), 1779 (γ-lactone) cm^{-1}.

1,5-cis-Guaianolide [**3**].—Compound **3**: $C_{15}H_{22}O_3$, mol wt 250, gum; eims *m/z* (% rel. int) $[M]^+$ 250 (77.7), $[M-Me]^+$ 235 (5.6), $[M-H_2O]^+$ 232 (3.2), $[M-Me-H_2O]^+$ 217 (3.2), $[M-Me-CO]^+$ 207 (47.1), 194 (14.6), 177 (29.8), 107 (34.5), 95 (37.5), 93 (40.2), 91 (46.5), 81 (48.4), 79 (51.9), 67 (45.2), 55 (100.0), 41 (71.3); ^{1}H-nmr (200 MHz) δ 2.40 (H-3a), 3.88 (d, H-6), 1.90 (H-7), 2.25 (H-10), 2.20 (H-11), 1.14 (d, 3H, H-13), 0.98 (d, 3H, H-14), 5.0 (d, H-15a), 5.08 (br s, H-15b); $J_{6,7}=9.9$, $J_{15,3}=1.0$, $J_{14,10}=J_{13,11}=7.2$.

Compressanolide {4α-Hydroxy-1α,5α,6β,7α,11β-H-guaian-10(14)-en-6,12-olide} [**4**].—Compound **4**: $C_{15}H_{22}O_3$, mol wt 250, gum; eims *m/z* (% rel. int.) $[M]^+$ 250 (3.0), $[M-Me]^+$ 235 (3.4), $[M-H_2O]^+$ 232 (10.7), $[M-Me-H_2O]^+$ 217 (3.7), $[M-C_3H_6O]^+$ 192 (8.8), $[M-C_3H_6O-Me-H_2O]^+$ 159 (14.3), $[C_9H_{11}]^+$ 119 (47.4), $[C_4H_7]^+$ 55 (44.7), $[MeCO]^+$ 43 (100.0); NH_3 cims $[M+NH_4]^+$ 268, $[MH]^+$ 251; ^{1}H nmr (400 MHz) δ 2.92 (ddddd, H-1), 1.70 (H-2α), 1.82 (H-2β), 2.10 (H-3α), 1.74 (H-3β), 2.20 (dd, H-5), 3.98 (dd, H-6), 1.70 (H-7), 1.19 (H-8α), 2.05 (dddd, H-8β), 2.58 (dddd, H-9α), 1.78 (H-9β), 2.17 (H-11), 1.18 (d, 3H, H-13), 4.92 (dddd, H-14a), 4.88 (dddd, H-14b), 1.23 (s, 3H, H-15); $J_{5,6}=J_{6,5}=11.7$, $J_{1,5}=J_{5,1}=11.5$, $J_{6,7}=9.8$, $J_{1,2\alpha}=10.2$, $J_{1,2\beta}=9.0$, $J_{8\alpha,8\beta}=13.0$, $J_{8\beta,7}=5.5$, $J_{8\beta,9\alpha}=J_{9\alpha,8\beta}=4.7$, $J_{8\beta,9\beta}=3.6$, $J_{9\alpha,9\beta}=13.0$, $J_{9\alpha,8\alpha}=3.7$, $J_{9,14}=1.0$ (COSY experiment was carried out at 400 MHz); ir ν max (neat) 3457 (OH), 1773 (γ-lactone), 1640 (C=C) cm^{-1}.

Dihydromichelliolide {4α-Hydroxy-5α,6β,7α,11β-H-guaian-1(10)-en-6,12-olide} [**5**].—Compound **5**: $C_{15}H_{22}O_3$, mol wt 250, colorless crystals, mp 124–127° [lit. (19) 127°]; eims *m/z* (% rel. int.) $[M]^+$ 250 (4.6), $[M-Me]^+$ 235 (4.4), $[M-H_2O]^+$ 232 (18.5), $[M-Me-H_2O]^+$ 217 (7.8), $[M-C_3H_6O]^+$ 192 (19.5), $[M-C_3H_6O-Me-H_2O]^+$ 159 (37.8), $[C_9H_{11}]^+$ 119 (100.0), $[C_4H_7]^+$ 55 (25.3), $[MeCO]^+$ 43 (46.3); ^{1}H nmr (200 MHz) δ 2.60 (br d, H-5), 3.80 (dd, H-6), 1.25 (d, 3H, H-13), 1.70 (br s, 3H, H-14), 1.30 (s, 3H, H-15); $J_{5,6}=J_{6,5}=9.7$, $J_{6,7}=9.7$, $J_{13,11}=6.8$ (COSY experiment was carried at 200 MHz); trichloroacetylcarbamate derivative ^{1}H nmr (200 MHz) δ 3.1 (d, H-5), 1.65 (s, 3H, H-15), 8.5 (NH).

m-CHLOROPERBENZOIC ACID (MCPBA) OXIDATION OF DIHYDROMICHELLIOLIDE [**5**].—A solution of 370 mg of **5** and 400 mg of mcpba in 20 ml of CH_2Cl_2 was left at room temperature for 70 h and worked up as described in the literature (1). Cc of the crude product over Si gel using $CHCl_3$ and increasing the polarity with Me_2CO afforded, in order of appearance, **9** (180 mg), **7** (30 mg), **6** and **8** (75 mg), and **10** (5 mg). Rechromatography of fractions containing **6** and **8** by preparative tlc over Si gel using cyclohexane–*n*-BuOH (1:1) provided **6** (25 mg) and **8** (20 mg).

Guaianolide 1(10)-β-epoxide [**9**].—Compound **9**: $C_{15}H_{22}O_4$, mol wt 266, colorless crystals, mp 130–135° [lit. (1) 111–113°]; eims *m/z* (% rel. int.) $[M]^+$ 266 (0.3), $[M-Me]^+$ 251 (2.9), $[M-H_2O]^+$ 248 (3.5), $[M-H_2O-Me]^+$ 233 (1.6), $[M-MeCO]^+$ 223 (2.6), $[M-C_3H_6O]^+$ 208 (4.7), $[M-C_3H_6O-H_2O]^+$ 190 (14.5), $[C_5H_7O_2]^+$ 99 (48.0), $[C_6H_9O]^+$ 97 (50.5), $[C_4H_7]^+$ 55 (34.7), $[MeCO]^+$ 43 (100.0); ir ν max (neat) 3532 (OH), 1779 (γ-lactone) cm^{-1}.

Cyclobutane-type lactone **7**.—Compound **7**: $C_{15}H_{22}O_4$, mol wt 266, gum; cims *m/z* (% rel. int.) $[M+H]^+$ 267 (87.2), $[M-H_2O+H]^+$ 249.1 (37.9), $[M-2H_2O+H]^+$ 231.1 (50.9), 219.1 (43.2), 203.2 (72.5), 193.2 (38.1), 175.2 (100.0), 147.2 (72.0), 245.2 (35.2), 133.2 (31.0), 119 (23.4), 95.1 (18.9), 55.1 (14.1); ir ν max (neat) 3459 (OH), 1771 (γ-lactone) cm^{-1}.

Guaianolide-1(10)-α-epoxide [**8**].—Compound **8**: $C_{15}H_{22}O_4$, mol wt 266, colorless crystals, mp 117–118°; eims *m/z* (% rel. int.) $[M]^+$ 266 (0.1), $[M-Me]^+$ 251 (0.8), $[M-H_2O+H]^+$ 249 (1.0), $[M-H_2O]^+$ 248 (0.5), $[M-H_2O-Me]^+$ 233 (0.8), $[M-MeCO]^+$ 223 (1.0), $[M-C_3H_6O]^+$ 208 (1.7), $[M-C_3H_6O-H_2O]^+$ 190 (2.0), $[C_5H_7O_2]^+$ 99 (17.6), $[C_6H_9O]^+$ 97 (23.8), $[C_4H_7]^+$ 55 (28.3), $[MeCO]^+$ 43 (100); ir ν max (neat) 3483 (OH), 1773 (γ-lactone) cm^{-1}.

Guaianolide-10(14)-α-epoxide [**6**].—Compound **6**: $C_{15}H_{22}O_4$, mol wt 266, colorless crystals, mp 192–193°; eims *m/z* (% rel. int.) $[M-Me]^+$ 251 (6.3), $[M-H_2O+H]^+$ 249 (1.9), $[M-H_2O]^+$ 248 (1.5), $[M-H_2O-Me]^+$ 233 (3.0), $[M-C_2H_3O]^+$ 233 (4.7), $[M-C_3H_6O]^+$ 208 (9.0), $[M-H_2O-C_2H_3O]^+$ 205 (9.8), 193 (17.6), 175 (9.2), 166 (18.9), 145 (16.5), 135 (23.8), 105 (37.1), 93 (100.0), 79 (54.8), $[C_4H_7]^+$ 55 (46.1), $[MeCO]^+$ 43 (70.1); ir ν max (neat) 3509 (OH), 1773 (γ-lactone) cm^{-1}.

Xanthanolide [**10**].—Compound **10**: $C_{15}H_{20}O_4$, mol wt 264, gum; cims *m/z* (% rel. int.) $[M+H]^+$ 265 (100.0), $[M-H_2O+H]^+$ 247 (52.4), $[M-H_2O-CO-H]^+$ 219 (13.5), $[M-2H_2O-CO+H]^+$ 201 (16.8); eims *m/z* (% rel. int.) $[M]^+$ 264 (1.5), 246 (2.8), 231 (1.4), 221 (2.3), $[M-C_3H_6O]^+$ 206 (100.0), 191 (32.3), 175 (8.9), 91 (27.5), 55 (38.4), $[MeCO]^+$ 43 (71.2); ir ν max (neat) 2928, 1773 (γ-lactone), 1715 (methyl ketone), 1701 (α,β-unsaturated ketone), 1653, 1647, 1385, 1169 cm^{-1}.

X-RAY EXPERIMENTAL.—Data collection was carried out on an Enraf-Nonius CAD4 diffractometer equipped with CuKα radiation (λ = 1.54184 Å) and a graphite monochromator, employing ω–2θ scans of variable rate.

CRYSTAL DATA.—exo-*Epoxide* **6**.—$C_{15}H_{22}O_4$, mol wt 266.3; orthorhombic space group $P2_12_12_1$; a = 9.1050(8), b = 11.025(4), c = 13.908(3) Å, V = 1396.1(9) $Å^3$, Z = 4, d_c = 1.267 g/cm^3, T = 22°, μ = 7.0 cm^{-1}, crystal size 0.36 × 0.44 × 0.60 mm.

1,10-epoxide **8**.—$C_{15}H_{22}O_4 \cdot H_2O$, mol wt 284.4; orthorhombic space group $P2_12_12_1$, a = 8.568(2), b = 10.4224(10), c = 16.581(2) Å, V = 1480.6(7) $Å^3$, Z = 4, d_c = 1.276 g/cm^3, T = 22°C, μ = 7.4 cm^{-1}, crystal size 0.08 × 0.12 × 0.52 mm.

One octant of data within $2°<\theta<75°$ was measured for **8**, two octants for **6**. Data reduction included corrections for Lorentz, polarization and background effects, and absorption corrections by Ψ scans. Minimum relative transmission coefficients were 94.22% for **6** and 87.92% for **8**. Of 2870 unique data for **6**, 2839 had I>O and were used in the refinement. For **8**, 1652 of 1746 unique data had I>O and were used in the refinement.

TABLE 4. Coordinates for **6**.

Atom	*x*	*y*	*z*
O-1	0.83162(8)	−0.11148(7)	0.53127(6)
O-2	0.9211(1)	−0.25880(9)	0.43920(8)
O-3	0.9524(1)	0.2831(1)	0.78352(8)
O-4	0.53275(9)	0.01235(9)	0.53710(8)
C-1	0.8198(1)	0.20972(9)	0.63808(9)
C-2	0.6792(2)	0.2507(1)	0.6908(1)
C-3	0.5543(1)	0.1849(1)	0.6413(1)
C-4	0.6166(1)	0.0600(1)	0.61557(9)
C-5	0.7754(1)	0.09224(9)	0.58218(7)
C-6	0.8872(1)	−0.00887(9)	0.58757(7)
C-7	1.0374(1)	0.0195(1)	0.54305(8)
C-8	1.1470(1)	0.0729(1)	0.6141(1)
C-9	1.1031(1)	0.1969(1)	0.6531(1)
C-10	0.9549(1)	0.2002(1)	0.70251(9)
C-11	1.0855(1)	−0.1036(1)	0.50296(8)
C-12	0.9427(1)	−0.1686(1)	0.48623(9)
C-13	1.1813(2)	−0.0990(1)	0.41331(9)
C-14	0.9456(2)	0.1546(2)	0.8013(1)
C-15	0.6109(1)	−0.0265(1)	0.7001(1)

Structures were solved by direct methods using MULTAN (41) and refined by full-matrix least squares based on F with weights $w = \sigma^{-2}(Fo)$, using the Enraf-Nonius SDP programs (42). Nonhydrogen atoms were treated anisotropically, while hydrogen atoms were located from difference maps and, except for those on the H_2O molecule of **8**, were refined isotropically. For **6**, R = 0.034 for 261 variables; for **8**, R = 0.042 for 270 variables. Absolute configurations were not determined. Coordinates are given in Tables 4 and 5.[3]

TABLE 5. Coordinates for **8**·H_2O.

Atom	*x*	*y*	*z*
O-1	0.4879(2)	0.6502(1)	0.8851(1)
O-2	0.3507(2)	0.8224(2)	0.8509(1)
O-3	0.9659(2)	0.4108(1)	0.95947(9)
O-4	0.6416(2)	0.3233(1)	1.02124(9)
C-1	0.8314(3)	0.4362(2)	0.9089(1)
C-2	0.7654(3)	0.3242(2)	0.8597(1)
C-3	0.5893(3)	0.3227(2)	0.8785(2)
C-4	0.5741(3)	0.3979(2)	0.9566(1)
C-5	0.6924(3)	0.5078(2)	0.9452(1)
C-6	0.6522(3)	0.6085(2)	0.8814(1)
C-7	0.7414(3)	0.7352(2)	0.8866(1)
C-8	0.9111(3)	0.7292(2)	0.8609(1)
C-9	1.0074(3)	0.6375(2)	0.9134(1)
C-10	0.9805(3)	0.4982(2)	0.8908(1)
C-11	0.6358(3)	0.8218(2)	0.8354(1)
C-12	0.4759(3)	0.7713(2)	0.8564(1)
C-13	0.6481(3)	0.9667(2)	0.8480(2)
C-14	1.0791(4)	0.4503(3)	0.8219(2)
C-15	0.4074(3)	0.4335(3)	0.9810(2)
O-1W	0.7795(4)	0.5782(2)	0.6774(1)

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[3]Atomic coordinates for structure **6** and **8** have been deposited with the Cambridge Crystallographic Data Center and can be obtained on request from Dr. Olga Kennard, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

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