DIKETONE CEMBRENOLIDES FROM THE
PACIFIC GORGONIAN *LOPHOGORGIA ALBA*

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Abstract—Three new diketone cembrenolides have been isolated from the Pacific sea whip *Lophogorgia alba*. The structure of lophodione (1) was assigned by X-ray crystallography, and isolophodione (2) and epoxylophodione (3) have been assigned based upon interconversion with (1) and by proton difference decoupling and nOe experiments. The previously reported neurotoxin, lophotoxin (4) was also isolated from *L. alba*. Since *L. alba* does not contain the endo-symbiotic algae (zooxanthellae), which are well-known in the Caribbean and Indo-Pacific corals, compounds 1–4 would appear to be of animal origin.

Gorgonian corals examined from the Caribbean Sea are known to contain novel cembrenolides as well as other terpenoid compounds. They also play host to large numbers of symbiotic algae (zooxanthellae) in their tissues. The role of zooxanthellae in the biogenesis of terpene derived compounds in gorgonians and other soft corals has recently been a subject under study and debate by both chemists and biologists.[1] We wish to report here the isolation of three new cembrenolide diketones from a Pacific gorgonian which lacks zooxanthellae,[2] indicating that zooxanthellae are not essential to the production of secondary metabolites in some gorgonian corals. *Lophogorgia alba* also contains the potent neuromuscular toxin, lophotoxin[3] (4), as well as other pukalide[4] (5)-related compounds which will be described in a separate paper. The three 1,4-diketones isolated may also represent possible precursors to this group of furan-containing cembrenolides.

The isomeric diketones 1 and 2 were isolated by repeated column and high performance liquid chromatography (hplc) of the chloroform/methanol extract of the pink sea whip, *Lophogorgia alba* (Duch. & Mich.), collected in Pacific Mexico. Both compounds were sensitive to silica gel chromatography; therefore florisil and rapid elution chromatography techniques were employed. Isolophodione (2) was found as the major terpenoid component (0.51% of the extract); while the corresponding isomer, lophodione (1), was less concentrated (0.36% extract). An epoxide isomer, epoxylophodione (3), was also a minor component.
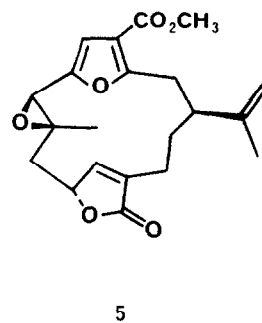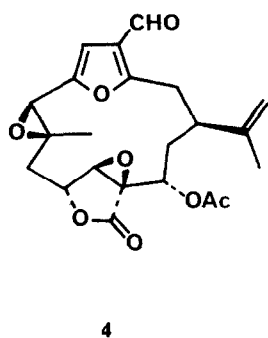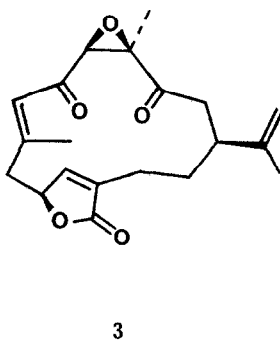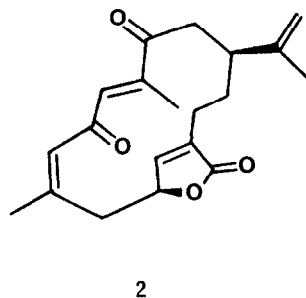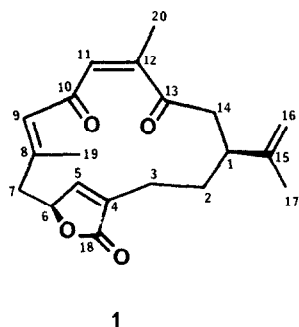
Lophodione (1) crystallized from one hplc fraction, m.p. = 172–174°, and the molecular formula, $C_{20}H_{24}O_4$, was obtained by a combination of low resolution mass and ^{13}C NMR spectrometry (Table 1). An IR absorption at 1751 cm^{-1} suggested an unsaturated γ-lactone, similar to that in pukalide[4] which was confirmed by ^1H NMR bands at δ6.97 (1H, bs) and 5.31 (1H, m) and ^{13}C NMR bands at 173.1 (s), 148.4 (d), 134.1 (s) and 80.1 (d) ppm. Additional IR absorptions at 1669 and 1616 cm^{-1} indicated the presence of an α,β-unsaturated ketone with

possible further conjugation, which was supported by the presence of two CO bands in the ^{13}C NMR spectrum at 190.7 (s) and 205.4 (s) ppm. Evidence for an enone with extended conjugation also came from the UV absorption at 267 nm (ε = 8000).

The α,β-unsaturated-γ-lactone, two CO's and three other olefins indicated by ^{13}C NMR provided eight of the nine degrees of unsaturation required by the molecular formula; therefore lophodione was monocarbocyclic. The presence of four Me vestiges in the ^{13}C and ^1H NMR spectra (the lactone CO plus three olefinic Me groups), combined with the results of ^1H NMR decoupling experiments, suggested that lophodione contained a cembrenolide ring system with an isopropenyl group and two trisubstituted olefins.

^1H NMR decoupling and nuclear Overhauser enhancement (nOe) experiments[5] allowed the stereochemistry of the two trisubstituted olefins to be determined.[6] Proton decoupling showed that the Me group at δ1.84 was coupled to the olefinic methine at δ6.42, and the Me group at δ2.19 was mutually coupled to the methine proton at δ6.12. Irradiation of the Me group at δ1.84 under nOe conditions resulted in an enhancement of 16% in the integrated intensity of the proton at δ6.42, thus indicating a *Z* configuration for the olefin. Irradiation of the Me group at δ2.19 under the same conditions did not result in significant enhancement in the proton at δ6.12. Therefore, the two groups are *trans* to one another, resulting in a *E* configuration for the second trisubstituted olefin.

Due to the predominant lack of distinguishable coupling in the ^1H NMR spectrum, we were not able to place the functional groups in the cembrenolide ring system or determine the relative stereochemistry at the two asymmetric centers in the molecule. Therefore, suitable crystals of lophodione (1) were submitted for X-ray diffraction analysis. The X-ray experiment defined the relative stereochemistry of both C(1) and C(6) as (*S*). The C(8)–C(9) double bond has the *E* configuration and the C(11)–C(12) configuration is *Z*. The double bonds

1

2

3

4

5

hold the 14-membered ring in a fairly open conformation as illustrated in Fig. 1. The enone containing C(8)–C(9)–C(10)–O(23) is completely conjugated as judged by a dihedral angle of 180°. The C(13)–O(24) CO shows little p-orbital overlap with the C(11)–C(12) double bond as recognized by the dihedral angle of 49°; and the C(10)–O(23) CO is also isolated from the C(11)–C(12) olefin with a dihedral angle of 42°.

Isolophodione (2) crystallized from one HPLC fraction, m.p. = 172–175°, and showed an identical molecular formula to lophodione, $C_{20}H_{24}O_4$, by high resolution mass and ^{13}C NMR spectrometry (Table 1). The same major structural features of lophodione (α,β-unsaturated-γ-lactone, two trisubstituted olefins, isopropenyl group and two ketones) were present in isolophodione by examination of the IR, UV, ^1H and ^{13}C NMR spectra; albeit with very slightly different chemical shifts (Tables 1 and 2). The strong correlation of all spectral data with 1 suggested that the two compounds could be geometrical isomers of one another at either or

both of the trisubstituted olefins. Isomerization of lophodione to isolophodione, and vice versa, was accomplished using iodine in benzene, providing confirmation of our proposal. However, the geometry of the two trisubstituted olefins in isolophodione was still in question: the C(8) E and C(11) Z olefins in lophodione could potentially isomerize to either the corresponding E,E; Z,Z or Z,E olefins.

Irradiation at $\delta2.04$ under ^1H NMR decoupling and nOe conditions caused considerable enhancement of the proton at $\delta6.26$, thus illustrating that one olefin was in the Z configuration. Similarly, irradiation at $\delta1.89$ yielded no enhancement at $\delta6.15$ which made it clear that the other trisubstituted olefin was in the E configuration. Therefore, in 2 both olefins had been isomerized (E,Z to Z,E). Irradiation of the two olefinic protons under nOe conditions resulted in enhancements which demonstrated their proximity in space, similar to that in lophodione, supporting the Z,E configuration.

The ring conformation of isolophodione is also similar ▸

to lophodione in that, based upon molecular models, it is possible for only one of the trisubstituted olefins to be conjugated with one of the ketones. Shifts in the ^{13}C NMR at 189.1 (s) and 208.3 (s) ppm, reflecting both a conjugated and a nonconjugated ketone,[7] substantiate this. The ^{13}C NMR data in Table 1 also supports this conformation by demonstrating the changes in polarization of the enone olefins in going from E to Z.[8]

In the course of repeated isolations of lophodione and isolophodione from extracts of *Lophogorgia alba*, one of

the related minor constituents found appeared to be very closely related to lophodione based on spectral data. Epoxylophodione (3) was determined to have a molecular formula of $C_{20}H_{24}O_5$ based on high resolution mass and ^{13}C NMR spectrometry (Table 1). The ^1H NMR of epoxylophodione was almost identical to that of lophodione, except for the absence of one olefinic methine and the appearance of a new epoxide methine at $\delta 3.47$. In addition, one of the singlet olefinic Me groups in lophodione was shifted upfield from $\delta 1.89$ to 1.58 in

Table 1. ^{13}C NMR data

C#	Lophodione (1)[a] ^{13}C ppm	J_R	Isolophodione (2)[a] ^{13}C ppm	J_R	Epoxylophodione (3)[b] ^{13}C ppm
1	41.3		40.5		42.8
2	30.3	16.1	31.2		31.0
3	25.7	16.7	22.2		22.9
4	134.1		133.1		135.7
5	148.4	37.3	148.6	37.5	147.6
6	80.1	28.9	77.9	25.2	79.5
7	43.5	18.9	37.3		42.1
8	156.3		146.4		157.9
9	125.9	31.2	128.0	33.6	123.2
10	190.7		189.0		192.7
11	133.4	32.5	126.5	31.0	65.6
12	144.8[c]		154.1		66.8
13	205.4		208.3		205.2
14	45.7	17.2	44.8		43.8
15	145.5[c]		146.4		146.4
16	115.9	27.7	114.0	26.8	111.9
17	17.0	16.0	19.1	15.4	19.1
18	173.1		173.1		173.1
19	22.6	18.5	26.9	17.8	22.8
20	21.5	16.7	22.2	16.0	19.4

[a] Assignments are based upon multiplicities, chemical shifts and residual coupling constants as determined by single frequency off-resonance and broad band decoupling techniques. Spectra were recorded on a Varian CFT-20 spectrometer in $CDCl_3$ with internal TMS. Measurement of the residual coupling constants for isolophodione were recorded in 75% $CDCl_3$/ benzene-d_6 solution.

[b] Assignments are based upon chemical shifts and proton substitution as determined by INEPT (insensitive nucleus enhancement phase transfer) methods, and two level broad band decoupling experiments. Spectra were recorded on a Nicolet 50 MHz ^{13}C multinuclear wide-bore spectrometer.

[c] Assignments may be reversed.

Table 2. ^{1}H NMR data[a]

C#	Lophodione (1) δ	Mult. J		Isolophodione (2) δ	Mult.	Epoxylophodione (3) δ	Mult. J	
1						2.71	m	
2						1.82	m	
						1.42	m	
3						2.43	m	
						2.24	m	
5	6.97	bs		7.00	bs	7.22	bs	
6	5.31	m		4.99	m	5.24	m	
7	3.04	dd	-13.3, 4.6	2.67	m	2.99	dd	-13.4, 4.6
	2.61	bd	-13.3	2.41	m	2.67	dd	-13.4, 3.2
9	6.12	bs		6.26	bs	6.23	bs	
11	6.42	bs		6.15	bs	3.47	s	
14	2.64	bd	-14.0			2.50	dd	-16.1, 6.8
	2.40	m				2.32	dd	-16.1, 7.3
16	4.97	bs		4.90	bs	4.79	bs	
	4.72	bs		4.70	bs	4.70	bs	
17	1.60	bs		1.68	bs	1.68	bs	
19	2.19	bs		2.04	bs	2.15	bs	
20	1.84	bs		1.89	bs	1.58	bs	

[a] Assignments are based on chemical shift, decoupling and nOe experiments.

^{1}H NMR spectra were recorded on a Varian HR 220 or 360 MHz spectrometers
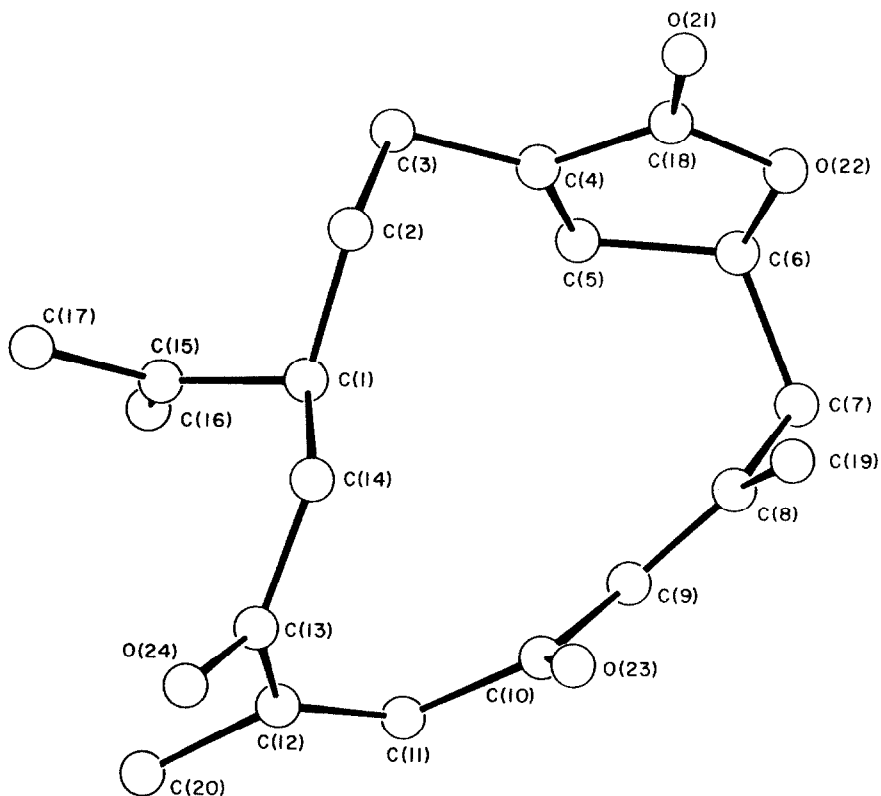
using $CDCl_3$ with TMS.

Fig. 1. A computer generated perspective drawing of lophodione (1). Hydrogens are omitted for clarity and no absolute stereochemistry is implied.

epoxylophodione. The absence of any alcoholic absorption in the IR spectrum, combined with the fact that both the shifted Me and methine protons in the ^{1}H NMR remained singlets, indicated that epoxylophodione was an epoxide derivative of one of the trisubstituted olefins in lophodione. ^{13}C NMR absorptions at 65.8 (d) and 66.8 (s) ppm supported this proposal, along with the high degree of correlation of the remaining ^{13}C NMR bonds (Table 1).

A ^{1}H NMR decoupling study of epoxylophodione allowed the clear delineation and assignment of every proton in the molecule, placing the position of the epoxide at C(11)–C(12). The C(8)–C(9) olefin was determined to be intact on the basis of strong correspondence in the chemical shifts and coupling characteristics to lophodione of the protons at C(6), C(7) and C(19) (Table 2). This correspondence was lacking in isolophodione, reaffirming our structural proposal. In addition, the IR absorption at 1736 cm^{-1}, indicating an isolated ketone, could only be accounted for by structure 3 for epoxylophodione.

A ^{1}H NMR nOe experiment was employed to define the stereochemistry of the epoxide and the remaining enone olefin of epoxylophodione. Irradiation of the Me group at $\delta 1.58$ resulted in an enhancement of the epoxide methine proton at $\delta 3.47$, indicating a Z epoxide. Lack of similar enhancement of the olefinic proton at $\delta 6.23$ after irradiation of the Me group at $\delta 2.15$ enabled us to assign the olefin at C(8)–C(9) as E. Irradiation of the olefinic methine proton at $\delta 6.23$, under nOe conditions, also produced an enhancement in the epoxide methine proton at $\delta 3.47$ ppm, indicating their proximity. A smaller enhancement was observed as a result of the reverse experiment. The demonstrated proximity of these two protons, combined with the strong similarities in the ^{13}C and ^{1}H NMR data, suggested the stereochemistry of the two asymmetric centers and the conformation of epoxylophodione to be identical to lophodione. Attempts to chemically interrelate the two compounds were not successful.

EXPERIMENTAL

General. IR spectra were recorded on a Perkin–Elmer 137 spectrophotometer and UV spectra were recorded on a Beckman MVI instrument. Low resolution mass spectra were obtained on a Hewlett–Packard Model 5930A mass spectrometer and high resolution mass spectra were obtained from the Department of Chemistry, Colorado State University on a AEI MS-902 instrument. Optical rotations were measured on a Perkin–Elmer 141 polarimeter with a one decimeter microcell. All solvents were redistilled prior to use.

Collection, extraction and isolation. Lophogorgia alba. (Duch. & Mich.), collection PG#74, was collected by hand using SCUBA in June 1978 at Bahia Tenacatita during the R.V. Alpha Helix cruise to Pacific Mexico. Repeated extraction of the ground animal (6.5 kg dry weight) with 70% chloroform/methanol was followed by removal of the solvents under vacuum. The aqueous residue obtained was partitioned between CHCl$_3$ and water. The organic layer was dried over MgSO$_4$ and concentrated to give 230 gm of crude extract. A mixture of lophodione, isolophodione and epoxylophodione was eluted from a silica gel column using 60–100% CHCl$_3$/petroleum ether, and the mixture was further purified using florisil chromatography.

Lophodione (1). The 8(E), 11(Z) isomer was eluted from a florisil column using 80–100% CHCl$_3$/petroleum ether and purified by silica hplc (5μ silica column, 50% ethyl acetate in isooctane). Recrystallization from EtOAc/isooctane yielded 0.142 g of 1, m.p. = 172–174°, $[\alpha]_D^{23} = -274.6$ (c 0.8, CHCl$_3$), (0.36% extract). Lophodione exhibited the following spectral

features: UV: $\lambda_{max}^{MeOH} = 267$ nm ($\epsilon = 8000$); IR (CHCl$_3$): 2950, 1751, 1669, 1616, 1433, 1202, 1115 cm^{-1}; MS: M$^+$ m/e 328 for C$_{20}$H$_{24}$O$_4$ (low resolution), 232, 178, 151.

Isolophodione (2). The 8(Z), 11(E) isomer was eluted from a florisil column with 60–80% CHCl$_3$/petroleum ether and purified by silica hplc (5μ silica column, 45% ethyl acetate in isooctane) to give white crystals $[\alpha]_D^{18} = -231.8°$ (c 1.0, CHCl$_3$), m.p. = 172–175°, (0.51% extract). Isolophodione exhibited the following spectral characteristics: UV: $\lambda_{max}^{MeOH} = 261$ nm ($\epsilon = 10,000$); IR (CHCl$_3$): 2941, 1754, 1675, 1618, 1439, 1208, 1115 cm^{-1}; MS: M$^+$ obs. 328.1679, calc. 328.1675, for C$_{20}$H$_{24}$O$_4$, M$^+$–C$_5$H$_4$O$_2$ obs. 232.1464, calc. 232.1463, M$^+$–C$_9$H$_{10}$O$_2$ obs. 178.1002, calc. 178.0994, M$^+$–C$_{11}$H$_{13}$O$_2$ obs. 151.0764, calc. 151.0759.

Epoxylophodione (3). The 8(E), 11(Z) epoxide was separated from a mixture of 1 and 2 on florisil using 60% CHCl$_3$/petroleum ether and purified by silica hplc (5μ silica column, 50% EtOAc in isooctane) to produce 0.013 g of a noncrystalline white solid $[\alpha]_D^{23} = -114.4°$ (c 1.1, CHCl$_3$). Epoxylophodione exhibited the following spectral features UV: $\lambda_{max}^{MeOH} = 250$ nm ($\epsilon = 13,000$); IR (CHCl$_3$): 3021, 1757, 1736, 1678, 1613, 1443, 1241 cm^{-1}; MS: M$^+$ obs. 344.1605, calc. 344.1624 for C$_{20}$H$_{24}$O$_5$.

X-Ray crystallographic study of lophodione (1). Preliminary X-ray photographs of single crystals of lophodione showed monoclinic symmetry. Accurate cell constants, determined by a least-squares fit of 15 diffractometer-measured 2θ values between sin θ/λ values of 0.14 to 0.20 Å^{-1}, where $a = 6.329(2)$, $b = 13.925(8)$, $c = 10.438(7)$ Å and $\beta = 105.20(4)°$. A rough experimental and calculated ($Z = 2$) density of 1.23 g/cm^3, systematic extinctions (0k0, k = 2n + 1 missing) and the known chirality were uniquely accommodated by space group P2$_1$ with one molecule of composition C$_{20}$H$_{24}$O$_4$ in the asymmetric unit. All unique diffraction maxima with $2\theta \le 114°$ were surveyed on a computer-controlled, four-circle diffractometer using graphite monochromated CuK$\bar\alpha$ radiation (1.54178 Å) and a 1°, variable speed ω-scan technique. Of the 1632 reflections examined, 1581 (97%) were judged observed [$|F_0| \ge 3\sigma(F_0)$] after correction for Lorentz, polarization and background effects.

A phasing model was uneventfully achieved using a multisolution weighted tangent formula approach.[9] An E-synthesis of the most favorable solution revealed the entire nonhydrogen structure of the molecule.[10] After partial refinement a ΔF-synthesis showed most of the H positions and the remainder were included at anticipated positions. Full-matrix least-squares refinements with anisotropic temperature factors for the nonhydrogen atoms have converged to a standard crystallographic residual of 0.053 (wR = 0.072) for the observed reflections. A final ΔF-synthesis revealed no large residual peaks and no abnormally short intermolecular contacts were observed. The availability of additional crystallographic information is summarized in Ref. 12.

Isomerization of lophodione to isolophodione. Five drops of a soln containing one small crystal of I$_2$ dissolved in 10 ml benzene were added to 10 mg of lophodione in 2 ml EtOAc. Partial conversion to isolophodione was seen after 12 hr by tlc examination. The reaction was quenched using 5 ml of an aqueous sodium dithionate soln and extracted using EtOAc. The organic layer was dried over MgSO$_4$ and concentrated under reduced pressure to yield a 3:1 mixture of lophodione and isolophodione by 220 MHz ^{1}H NMR.

Isomerization of isolophodione to lophodione. Five drops of a soln of I$_2$ in benzene (see preceding) was added to 5 mg of isolophodione in 2 ml EtOAc. After fifteen minutes, conversion of lophodione was noted by tlc and the reaction was quenched and worked up as above. ^{1}H NMR analysis of the purified products showed an equimolar mixture of lophodione and isolophodione.

NOE study of lophodione (1). 3 mg (0.009 M) of lophodione in 1 ml of 0.5% TMS/CDCl$_3$ was carefully degassed by bubbling Ar through the soln for 60 min and the NMR tube was sealed with parafilm. ^{1}H NMR decoupling experiments identified the two pairs of vicinal Me and vinylic constituents. The methine proton at $\delta 6.42$ was coupled to the Me group at $\delta 1.84$, and the protons at $\delta 6.12$ and 2.19 were also coupled. The decoupler power was then decreased until the irradiated peaks were barely nulled. The

decoupler was gated for on delay only and the delay time between irradiations was increased from 2 to 20 sec. A sequence of 30 irradiations was performed alternating off resonance irradiations with irradiations of each of the four resonances under consideration; providing 3 replicates of each olefinic Me or proton irradiation. Enhancements were calculated by comparing the intensity of an olefinic absorption during each irradiation with its intensity under off resonance conditions set to 100%. An enhancement greater than 10% over the off resonance intensity was considered a positive result indicating proximity of two groups involved of 3.0 Å or less. Summary of the nOe experiments results: irradiation at $\delta 6.12$ resulted in an increase of 11% in the peak at $\delta 6.42$. Irradiation of the Me group at $\delta 1.84$ produced an increase of 16% in the methine/proton at $\delta 6.42$. Therefore, the protons at $\delta 6.42$ and 1.84 are *cis*, indicating a Z olefin, which places these absorptions at C(11) and C(20), using the X-ray data.

NOE study of isolophodione (**2**). 4 mg (0.012 M) of isolophodione in 1 ml of 0.5% TMS/CDCl$_3$ was prepared for a nOe experiment as above. An ^{1}H NMR decoupling study revealed that the vinylic proton at $\delta 6.26$ was coupled to the methyl group at $\delta 2.04$, and the protons at $\delta 6.15$ and $\delta 1.89$ were mutually coupled. The nOe experiment was executed and interpreted in the same manner as before. Difference nOe techniques[11] were also employed. Results: irradiation of the proton at $\delta 6.26$ produced a nOe enhancement in the proton at $\delta 6.15$ by difference nOe, indicating their proximity (~ 3.0 Å apart as measured using molecular models). Irradiation of the methyl group at $\delta 2.04$ resulted in a positive enhancement of 29% in the olefinic methine at $\delta 6.26$ indicating their *cis* relationship. No other significant enhancements were observed which placed the Z olefin at C(8) and C(9).

NOE study of epoxylophodione (**3**). 4 mg (0.012 M) of epoxylophodione in 1 ml 0.5% TMS/CDCl$_3$ was prepared for an nOe experiment as previously discussed. An ^{1}H NMR decoupling study showed that the olefinic proton at $\delta 6.23$ was coupled to the Me group at $\delta 2.15$, and the protons at $\delta 3.47$ and $\delta 1.58$ were mutually coupled. The nOe experiment was run and interpreted as previously discussed. Summary of nOe results: irradiation of the methine proton at $\delta 6.23$ resulted in a positive enhancement of the epoxide methine proton at $\delta 3.47$ of 11%. Irradiation in the reverse direction produced a smaller enhancement of 5%; however, still supporting their proximity in space (2.7 Å as measured using molecular models). Irradiation of the epoxide methyl group at $\delta 1.58$ caused an enhancement of 10% in the epoxide methine at $\delta 3.47$, indicating their *cis* relationship. No other significant nOe enhancements were observed, indicating that the epoxide at C(11)–C(12) was Z, with epoxylophodione possessing a very similar conformation to that of lophodione.

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