Articles

Longithorones, Unique Prenylated Para- and Metacyclophane Type Quinones from the Tunicate *Aplidium longithorax*

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A group of nine farnesylated quinones (**1**−**9**) featuring new macrocyclic skeletons formed by farnesyl units bridging the quinones in the meta or para positions have been isolated from a tunicate, *Aplidium longithorax*. Three of these are monomeric C_{21} compounds, while the remainder are dimeric C_{42} products. These meta- and paracyclophane type compounds all show atropisomerism and their biogenesis appears to involve 4 + 2 cycloadditions. Structures were determined by X-ray and spectroscopic analysis.

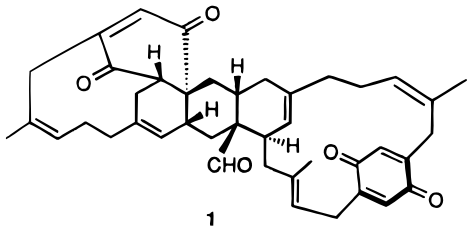
Introduction

Tunicates have become noted as sources of a broad spectrum of natural products among which cyclic peptides and alkaloids are the most common.[1,2] Included among these are the ecteinascidins,[3] potent anticancer drug candidates. Tunicates of the genus *Aplidium* have yielded prenylated hydroquinones and quinones,[4] terpenoids,[5] alkaloids,[6] nucleosides,[7] and bryostatin 4 and 5.[8] Of the approximately one dozen prenylated quinones or hydroquinones isolated from *Aplidium* or other tunicates, the most complex is longithorone A, **1**, from the tunicate *Aplidium longithorax* (Monniot) which we reported recently.[9] Longithorone A contains an unprecedented carbocyclic skeleton featuring a [12]paracyclophane moiety. A plausible biogenesis involves both intra- and intermolecular Diels−Alder reactions. Further analysis of *A. longithorax* has led to the isolation of eight related, novel cyclofarnesylated quinones (**2**−**9**). All nine of the longithorones have restricted rotations in their macrocyclic rings resulting in atropisomerism. Two bromodiphenyl ethers, **10** and **11**,[10] were also isolated; these are uncommon metabolites for tunicates. We report here the structure elucidation of the quinones longithorone B-I (**2**−**9**).

Results and Discussion

The MeOH and MeOH−CH_2Cl_2 (1:1) extracts of frozen specimens were concentrated and subjected to solvent partitioning[11] to furnish hexane, CH_2Cl_2, n-BuOH, and H_2O soluble fractions. The hexane fraction was chromatographed over a silica gel open column using hexane with increasing amounts of EtOAc. Selected fractions from this chromatography and also the crude CH_2Cl_2 soluble fraction were rechromatographed over silica gel and reversed phase HPLC repeatedly to yield longithorones A-I (**1**−**9**). Several fractions from the original chromatography of the hexane solubles were rechromatographed on a C-18 column to yield bromodiphenyl ethers **10** and **11**. The longithorones are all unstable in varying degrees, especially in $CDCl_3$ which was initially used for NMR analysis.

Monomeric Prenylated Quinones. Longithorone B (**2**), mp 80−82 °C, $[\alpha]_D$ −92.4° (*c* 0.57, CH_2Cl_2), $C_{21}H_{26}O_2$ by HREIMS,[12] showed 21 resonances in its ^{13}C NMR spectrum which according to a DEPT spectrum were associated with three methyl, six methylene, five methine, and seven quaternary carbons. UV absorption at 258 nm, strong IR absorption at 1649 cm^{-1}, ^{13}C NMR signals at δ 187.8 (s) and 188.1 (s), and one-proton ^1H NMR singlets at δ 6.23 and 6.45 indicated a *para*-disubstituted benzoquinone as in **1**. The ^{13}C NMR data further showed the presence of three trisubstituted double bonds (Table 1), thus requiring one carbocycle in addition to the quinone ring. Information gleaned from COSY, RCT-COSY, HMQC, and HMBC spectra (Table 1) led to formulation of structure **2** for longithorone B, and this was confirmed by X-ray crystallographic analysis.[24]



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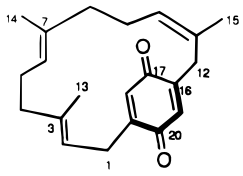

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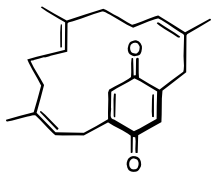

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A perspective ORTEP plot of **2** is shown in Figure 1. The molecule contains a 16-membered carbocycle comprised of benzoquinone bridged across the para position

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Table 1. NMR Data for Longithorone B (2) and Longithorone C (3)[a]

	longithorone B				longithorone C		
position	^{13}C (mult)[b]	^{1}H (mult, *J* in Hz)[c]	HMBC (C no.)	NOE correlations[d]	^{13}C (mult)[b]	^{1}H (mult, *J* in Hz)[c]	NOE correlations[d]
1β	29.1 (t)	3.33 (dd, 11.9, 8.1)	2, 3, 19	1α, 2	28.7 (t)	3.31 (ddd, 8.0, 15.4, 1.5)	1α, 2, 4
1α		2.45 (dd, 11.9, 8.1)	2, 3, 20	1β, 18, 13		2.58 (ddd, 8.0, 15.4, 1.5)	1β, 2, 18
2	122.1 (d)	5.40 (t, 8.1)	4, 13	1β, 5	120.9 (d)[f]	5.53 (t, 8.0)	1α, 1β, 13
3	138.5 (s)				139.1 (s)		
4	39.0 (t)	1.94 (m)		13	27.9 (t)	1.95 (m)	1β, 6, 18
5	24.1 (t)	1.94 (m)		2, 6	24.1 (t)	1.98 (m)	
6	122.6 (d)	4.73 (br m)	14	5, 8b	123.2 (d)[f]	4.70 (td, 7.0, 1.0)	4, 8b
7	135.2 (s)				135.2 (s)		
8a[e]	39.5 (t)	1.87 (m)		8b, 10, 14	39.7 (t)	1.95 (m)	
8b[e]		1.73 (m)		6, 8a		1.75 (m)	6
9a	29.2 (t)	1.89 (m)			30.3 (t)	1.93 (m)	
9b		1.45 (m)				1.65 (m)	12α
10	127.4 (d)	5.10 (dm, 10.5)	12, 15	8a, 15	126.7 (d)	5.10 (td, 8.0, 1.5)	15
11	130.9 (s)				132.1 (s)		
12α	32.1 (t)	3.46 (dd, 18.6, 1)	10, 15, 16, 21	12β	32.9 (t)	3.44 (br d, 17.0)	9b, 12β
12β		2.44 (dd, 18.6, 2.4)	10, 15, 16, 17, 21	12α		2.34 (br d, 17.0)	12α, 21
13	14.6 (q)	1.33 (s)	2, 3, 4	1α, 4, 18	22.2 (q)	1.54 (s)	2
14	15.6 (q)	1.38 (s)	7, 8	8a	16.0 (q)	1.39 (d, 1.0)	
15	26.5 (q)	1.63 (s)	10, 11, 12	10	27.2 (q)	1.70 (s)	10, 21
16	148.3 (s)				149.0 (s)[g]		
17	187.8 (s)				187.2 (s)[h]		
18	130.2 (d)	6.23 (d, 1)	17, 19, 20	13, 1α	132.9 (d)[i]	6.38 (t, 1.5)	1α, 4
19	147.8 (s)				149.4 (s)[g]		
20	188.1 (s)				187.4 (s)[h]		
21	132.4 (d)	6.45 (t, 1.9)	12, 20		133.1 (d)[i]	6.38 (t, 1.5)	12β, 15

[a] Spectra were recorded in C_6D_6. [b] ^{13}C NMR at 125 MHz, referenced to C_6D_6 (δ 128), multiplicities determined by DEPT experiment. [c] ^{1}H NMR at 500 MHz, referenced to residual solvent C_6D_6 (δ 7.20). [d] Data obtained from NOESY experiment with mixing time = 0.5 s. [e] The letters a and b designate different protons where the relative stereochemistry could not be assigned. [f–i] Signals with the same letters may be interchanged.

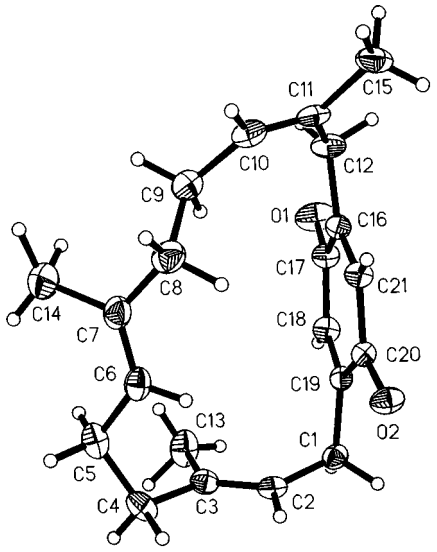

Figure 1. A perspective ORTEP plot of compound **2**. Thermal ellipsoids are plotted at the 35% probability level.

by a farnesyl unit having two *trans* (C2−C3 and C6−C7) and one *cis* (C10−C11) double bonds as in one of the farnesylated benzoquinone units of longithorone A (**1**).[9] However, the overall conformation of the 16-membered macrocycle in the present structure is different from that observed in longithorone A. The benzoquinone ring of **2** is rotated by about 140° compared to that in longithorone A. The absolute configuration was not determined.

The optical activity observed for longithorone B (**2**) which has no chiral centers revealed that there is restricted rotation in the macrocyclic ring and hence **2** represents one of the atropisomers possible for this skeleton. Observation of an NOE between H-13 and H-18 confirms that the solution conformation is similar to that in the solid state as elucidated by X-ray analysis. Heating of **2** in toluene at 80 °C for 1 h did not alter the optical rotation nor the ^{1}H NMR spectrum. Heating at 110 °C caused sample decomposition.

Longithorone C (**3**), $[\alpha]_D = -15.0°$ (*c* 0.07, CH_2Cl_2), was assigned the molecular formula $C_{21}H_{26}O_2$ from mass spectral and ^{13}C NMR data, the latter consisting of 21 resolved signals corresponding to three methyl, six methylene, five methine, and seven quarternary carbons (DEPT). The LR EIMS[12] showed a molecular ion peak at *m/z* 310. The IR and UV spectra of **3** were similar to those of **2**. The ^{1}H and ^{13}C NMR data (Table 1) closely resembled that of **2**, and COSY, LR-COSY, and RCT-COSY spectra of **3** revealed that the two compounds have

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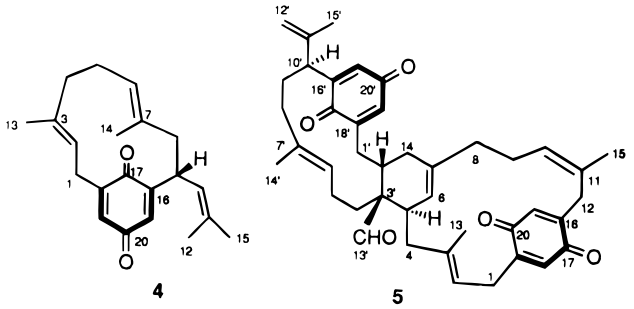
(12) Quinones and iminoquinones often show prominent M + 2 ions corresponding to their reduced form in EIMS[4b,13a] analysis, but some quinones show only the expected molecular ions.[13b] The EIMS of the quinones **2**−**4** revealed solely molecular ions, while the EIMS of compounds **5**−**8** displayed ions due to the reduced form. Similarly the FABMS of some quinones and iminoquinones are reported to show a cluster of peaks around (M^+) due to the reduced form while others do not.[13b]

the same skeletal connectivities. The difference in structure between **2** and **3** was traced to a difference in one double bond configuration, 2*Z* in **3** *vs* 2*E* in **2**. This was evident from the NOE observed between H-2 and H-13 in **3** as well as the downfield shift of C-13 in **3** relative to that observed in **2** (Table 1). Thus longithorone C was assigned structure **3**, and its optical activity is also due to atropisomerism.

Longithorone D (**4**), mp 127−9 °C, $[\alpha]_D = -305.3°$ (*c* 0.23, CH_2Cl_2), was assigned the formula $C_{21}H_{26}O_2$ based on HREIMS data: *m*/*z* 310.1925 (Δ mmu 0.8). The ^{13}C NMR spectra (proton noise decoupled and DEPT) revealed 21 signals (Table 2), corresponding to four methyl, four methylene, six methine, and seven quarternary carbons including two carbonyl carbons (δ 187.6 and 188.8). The presence of a 1,4-benzoquinone was evident from the UV absorption at 256 nm, an IR band at 1655 cm^{-1}, and the ^{13}C NMR peaks at δ 187.6 and 188.8. The 1,4-benzoquinone ring was found to be meta disubstituted, as was clearly demonstrated by the small coupling (*J* = 2.8 Hz) between the signals at δ 6.00 and 6.34 (COSY).



Interpretation of the COSY, LR-COSY, RCT-COSY, NOESY, HMQC, and HMBC spectra led to structure **4** for longithorone D and the NMR assignments in Table 2. The structure was confirmed by X-ray analysis.[24] NOE data (Table 2) indicate that the solution conformation of **4** closely resembles that of the solid state. A perspective ORTEP drawing of **4** is shown in Figure 2. The absolute configuration was not determined. The structure is closely related to the "primed" farnesylated benzoquinone unit of longithorone E (**5**) possessing a meta-bridged benzoquinone. However, the alkyl macrocycle is 12-membered in **4** compared to 13-membered in longithorone E (**5**).

Dimeric Prenylated Quinones. Longithorone E (**5**) was obtained as pale, yellow, fine needles, mp >230 °C dec, $[\alpha]_D = -35.4°$ (*c* 0.48, $CHCl_3$). The EIMS of longithorone E (**5**) exhibited ions at *m*/*z* 634 and 636 corresponding to $[M + 2]^+$ and $[M + 4]^+$ which are attributable to reduction of the quinone ring(s) during mass analysis.[12] The low-resolution FABMS contained a series of ions centered around *m*/*z* 634 $[(M + 2)^+]$.[12,13b] A DEPT experiment confirmed the presence of four methyls, twelve methylenes, twelve methines, one of which was an aldehyde carbonyl, and fourteen quarternary carbons including four carbonyl groups. These data, in combination with HRFABMS, confirmed a molecular formula $C_{42}H_{48}O_5$ for **5**. Analysis of ^1H and ^{13}C NMR data

Table 2. NMR Data for Longithorone D (4)[a]

position	^{13}C (mult)[b]	^1H (mult, *J* in Hz)[c]	HMBC (C no.)	NOE correlations[d]
1α	29.5 (t)	3.13 (ddd, 14.3, 8.6, 1.9)	2, 3, 18, 19	1β, 2
1β		2.35 (dd, 14.3, 7.2)	2, 18, 19	1α, 19
2	121.7 (d)	5.47 (t, 7.2)	1, 4, 13	1α, 4
3	139.6 (s)			
4	39.7 (t)	1.87 (m)		2, 6
5a[e]	25.4 (t)	1.98 (m)		5b
5b[e]		1.78 (br d, 14.8)		5a
6	131.5 (d)	4.79 (br d, 9.1)	4, 5, 8, 14	4, 8a
7	131.4 (s)			
8a	44.1 (t)	2.87 (dd, 13.4, 11.4)	7, 9, 10, 14	6, 8b, 9, 10
8b		2.29 (m)	7	8a, 9
9	43.5 (d)	3.41 (ddd, 11.4, 9.1, 6.7)	8, 10, 11, 16	8a, 8b, 12, 14, 21
10	126.6 (d)	5.86 (br d, 9.1)	8, 12, 15	8a, 15
11	132.6 (s)			
12	17.7 (q)	1.48 (d, 1.4)	10, 15	9, 21
13	15.4 (q)	1.12 (s)	2, 3, 4	19
14	14.2 (q)	1.29 (s)	6, 8	21
15	25.9 (q)	1.62 (d, 1.0)	10, 11, 12	10
16	151.7 (s)			
17	187.6 (s)			
18	149.3 (s)			
19	129.6 (d)	6.00 (dd, 2.8, 1.9)	1	1β, 13
20	188.8 (s)			
21	133.1 (d)	6.34 (d, 2.8)	9	9, 12, 14

[a] Spectra were recorded in C_6D_6. [b] ^{13}C NMR at 125 MHz, referenced to C_6D_6 (δ 128), multiplicities determined by DEPT experiment. [c] ^1H NMR at 500 MHz, referenced to residual solvent C_6D_6 (δ 7.20). [d] Data obtained from NOESY experiment with mixing time = 0.5 s. [e] The letters a and b designate different protons where the relative stereochemistry could not be assigned.

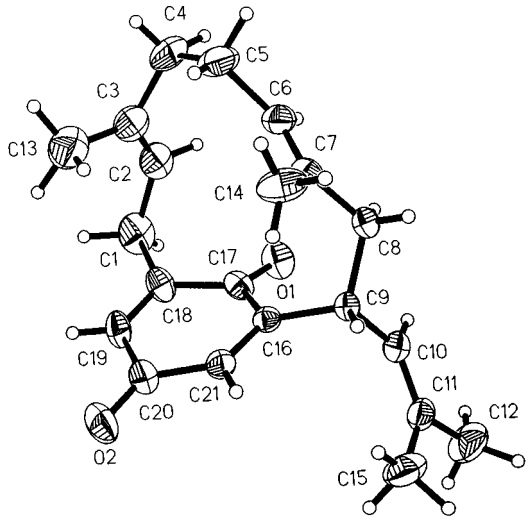


Figure 2. A perspective ORTEP plot of compound **4**. Thermal ellipsoids are plotted at the 35% probability level.

(Table 3) revealed that **5** contained eight trisubstituted and one disubstituted carbon−carbon double bonds and five carbonyl groups, hence requiring the presence of five carbocycles to satisfy the 19 degrees of unsaturation deduced from molecular formula. Two of five rings were accounted for by two disubstituted 1,4 benzoquinones, indicated by UV absorption at 258 nm, a strong IR band at 1654 cm^{-1}, and ^{13}C resonances at δ 186.4, 187.0 (2C), 187.1.[14] One of the 1,4-benzoquinones was deduced to be para substituted from the presence of two singlet

(13) For MS of quinones and iminoquinones: (a) Das, B. C.; Lounasma, M.; Tendilla, C.; Lederer, E. *Biochem. Biophys. Res. Commun.* **1965**, *21*, 318. (b) Blunt, J. W.; Munro, M. H. G.; Battershill, C. N.; Copp, B. R.; McCombs, J. D.; Perry, N. B.; Prinsep, M.; Thompson, A. M. *New J. Chem.* **1990**, *14*, 761.

(14) In the ^{13}C NMR spectrum of **5** in C_6D_6 only 3 peaks were displayed at about δ 187, while in $CDCl_3$ 4 signals were observed at δ 186.49, 187.34, 187.46, and 187.55.

Table 3. NMR Data for Longithorone E (5)[a]

position	^{13}C (mult)[b]	^{1}H (mult, *J* in Hz)[c]	HMBC (C no.)	NOE correlations[d]
1α	27.8 (t)	3.70 (t, 11.3)	2, 3, 18, 19	1*β*, 13
1*β*		2.18 (m)		1α, 2, 18
2	125.9 (d)	4.65 (dd, 11.3, 5.2)		1α, 4b, 18
3	135.8 (s)			
4a[e]	40.1 (t)	2.30 (m)	2, 3	4b
4b[e]		1.70 (m)		2, 4a, 13′
5	37.4 (d)	2.30 (m)	6	6, 13, 1′α, 4′a
6	120.4 (d)	5.00 (br s)	3′, 4, 5, 8, 14	5, 9a, 9b, 13
7	134.4 (s)			
8	37.8 (t)	1.72 (m)		
9a	26.5 (t)	2.08 (m)		6, 9b, 10
9b		1.75 (m)		9a
10	126.6 (d)	5.12 (m)		9a, 15
11	132.3 (s)			
12*β*	35.4 (t)	3.09 (dd, 16.5, 1.5)	10, 11, 15, 16	12α
12α		2.56 (br d, 16.5)	10, 11, 16, 17	12*β*, 21
13	15.1 (q)	1.77 (s)	2, 3, 4	1α, 5, 6
14a	37.3 (t)	2.47 (br d, 18.0)		2′, 13′, 14b
14b		1.52 (br d, 18.0)	3′, 6	14a
15	27.5 (q)	1.88 (s)	10, 11	10
16	149.5 (s)			
17	186.4 (s)			
18	131.5 (d)	6.24 (br s)	1, 16, 17, 19	1*β*, 2
19	147.8 (s)			
20	187.0 (s)			
21	133.5 (d)	6.31 (d, 1.2)	16, 19, 20	12α
1′α	29.5 (t)	3.05 (dd, 15.0, 6.7)	2′, 3′, 18′, 19′	5, 1′*β*, 4′b
1′*β*		1.32 (br d, 15.0)	18′, 19′	1′α, 19′
2′	39.2 (d)	2.18 (m)		14a, 19′
3′	52.8 (s)			
4′a	30.9 (t)	2.08 (m)		5, 4′b
4′b		1.17 (t, 13.5)		1′α, 4′a
5′a	21.1 (t)	1.87 (m)		5′b, 14′
5′b		1.66 (m)		5′a
6′	130.4 (d)	4.72 (br d, 7.6)	4′, 5′, 14′	8′b, 5′, 10′
7′	135.4 (s)			
8′a	40.5 (t)	1.89 (m)		8′b, 9′
8′b		1.80 (m)		6′, 8′a, 10′
9′	32.2 (t)	1.62 (m)		8′a, 10′, 12′a, 14′
10′	43.4 (d)	3.54 (br d, 9.5)	9′, 11′, 12′, 21′	6′, 8′
11′	147.3 (s)			
12′a	111.1 (t)	4.90 (br s)	10′, 15′	9′, 10′, 12′b, 21′
12′b		4.76 (br s)	10′, 15′	12′a, 15′
13′	204.6 (d)	9.47 (s)	3′	4b, 14a
14′	15.4 (q)	1.10 (s)	6′, 7′	5′a, 9′, 21′
15′	21.4 (q)	1.59 (s)	10′, 11′, 12′	12′b, 21′
16′	151.2 (s)			
17′	187.0 (s)			
18′	151.9 (s)			
19′	134.0 (d)	6.40 (t, 2.4)	1′, 21′, 17′	1′*β*, 2′
20′	187.1 (s)			
21′	130.4 (d)	6.44 (d, 2.4)	10′, 18′, 20′	14′, 15′, 12′a

[a] Spectra were recorded in C_6D_6. [b] ^{13}C NMR at 125 MHz, referenced to C_6D_6 (*δ* 128), multiplicities determined by DEPT experiment. [c] ^{1}H NMR at 500 MHz, referenced to residual solvent C_6D_6 (*δ* 7.20). [d] Data obtained from NOESY experiment with mixing time = 0.5 s. [e] The letters a and b designate different protons where the relative stereochemistry could not be assigned.

proton signals at *δ* 6.24 and 6.31, and the other meta substituted, judging from two coupled proton doublets (J = 2.4 Hz)[15] at *δ* 6.40 and 6.44. The two benzoquinone moieties accounted for four of the oxygens in the molecular formula, and the fifth was due to an aldehyde group which was revealed by an IR absorption at 1714 cm^{-1}, a proton singlet at *δ* 9.47, and a ^{13}C resonance at *δ* 204.6 (d).

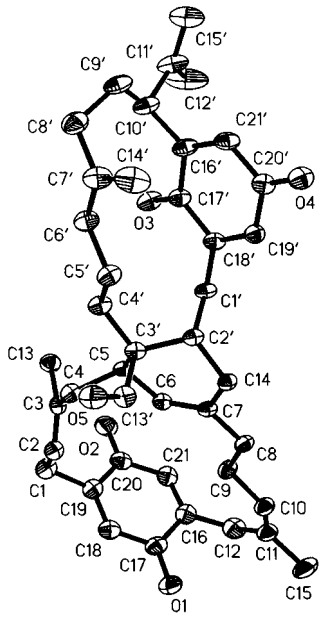


Figure 3. A perspective ORTEP plot of compound **5**. Thermal ellipsoids are plotted at the 35% probability level. Hydrogen atoms are removed for clarity.

Analysis of COSY, RCT-COSY, LR-COSY, HMQC, HMBC, and NOESY spectra revealed that the right half of **5** was identical to the right half of longithorone A (**1**), and the close correspondence of the carbon chemical shifts of the two compounds supported this. The planar structure of the remainder of structure **5** was also deduced from 2D NMR data with HMBC and long range H−H couplings providing the evidence for connecting the various fragments across the quaternary centers (Table 3). Long range H−H coupling between H-13′ and H-4′ provided evidence for connecting C-4′ to C-3′; no HMBC correlations to support this connection were observed. The double bonds were assigned as 2*E*, 10*Z*, and 6′*E* based on the chemical shifts for C-13 (*δ* 15.1), C-15 (*δ* 27.5), and C-14′ (*δ* 15.4) and also NOE data (Table 3). The relative stereochemistries of the chiral centers in the central six-membered ring and at C-10′ were also determined from NOESY data (Table 3). The structure and stereochemistry of **5** was confirmed by single-crystal X-ray diffraction[24] (Figure 3). The stereostructure of the central six-membered ring is consistent with a presumed Diels−Alder reaction in the biosynthesis. The NOE data reported in Table 3 indicate that the solution conformation of **5** is the same as that found in the solid state by X-ray analysis.

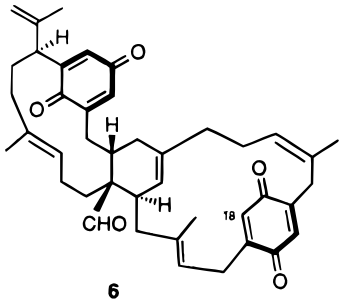
A perspective ORTEP drawing of longithorone E, **5**, is shown in Figure 3. The absolute configuration of longithorone E is presumed to be the same as that of longithorone A (**1**),[9] which was determined by X-ray diffraction because both compounds have negative rotations. Despite the *cis*-fusion at C2′−C3′, longithorone E is flatter than the more folded longithorone A (**1**). The

(15) The correlation of the two signals at *δ* 6.40 and 6.44 in both COSY and LR-COSY of longithorone E (**5**) in C_6D_6 is not unambiguous since the chemical shifts of those two signals are too close. However the COSY and LR-COSY of **5** taken in $CDCl_3$ revealed a very clear cross peak between those two signals which resonated at *δ* 6.63 (H-19′) and 6.42 (H-21′), respectively, in $CDCl_3$.

overall conformation of the 16-membered macrocycle is very similar in the two molecules, but it is different from the 16-membered alkyl macrocycle in longithorone B (**2**). The cyclohexene ring in **5** is in a half-chair conformation.

In the EIMS of **5** prominent ions were observed at *m/z* 308, 310 and 324, 326 corresponding to moieties resulting from reverse Diels−Alder fragmentation across the cyclohexene ring, the higher mass ion in each pair resulting from reduction of the quinone ring during mass analysis.

Longithorone F (**6**) was obtained as an amorphous powder, $[\alpha]_D = -65.2°$ (*c* 0.89, $CHCl_3$). The molecular formula $C_{42}H_{48}O_5$, which is identical with that of **5**, was assigned from high resolution FABMS and NMR spectral data (Table 4). The IR and UV spectra and ^{13}C NMR data of longithorone F were very similar to those of **5**. The EIMS of longithorone F (**6**) showed a molecular ion peak at *m/z* 632 and ions of the reduced form at *m/z* 634 and 636.[12] Prominent ions at *m/z* 308 and 324, which presumably derive from reverse Diels−Alder fragmentation, and the corresponding reduced forms *m/z* 310 and 326 were also observed. COSY, RCT-COSY, LR-COSY, NOESY, and HMQC data provided evidence for the same proton spin systems as in **5**. HMBC data (Figure 4 and Table 4) provided evidence for connecting the fragments to give structure **6** except for the connection of C-4′ to C-3′. Support for this connection came from a long range proton coupling detected between H-13′ and one of the H-4′ protons in a long range COSY experiment.



6

The NOESY data for **6** revealed that H-13 is spatially close to H-6, H-18, H-1α, and H-4a. Proton 1*β* showed NOE with H-2 and H-1α only. NOE correlation between H-13 and H-18 was also observed for compound **2** where the configuration was established by X-ray. On the other hand in the spectra of **1** and **5** H-13 showed NOE interaction with H-6 and H-1*β* (but not with H-18). Instead H-18 showed cross peaks with H-1α in NOESY spectra of **1** and **5**. Hence the C-13 methyl and C-18 of the *para*-disubstituted benzoquinone ring in **6** are both directed downward with respect to the plane of the macrocyclic ring as in **2** with H-18 close to H-13. Thus **5** and **6** are atropisomers. No isomerization of either isomer occurred as judged by NMR analysis when the samples were heated at 70 °C for 2 h.

Longithorone G (**7**), a minor component, was obtained as an amorphous powder, $[\alpha]_D = +73.5°$ (*c* 0.34, $CHCl_3$), and decomposed easily. The molecular formula $C_{42}H_{48}O_5$ was deduced from high resolution FABMS and NMR data (Table 5) and is identical to that of longithorone E (**5**) and F (**6**), indicating that all are isomers. After the ^1H and ^{13}C data of **7** had been assigned by analysis of its COSY, LR-COSY, RCT-COSY, HMQC, and HMBC spectra, it was obvious that the gross structure of longithorone G (**7**) was the same as that of longithorone F (**6**), and NOE data confirmed that the *para*-disubstituted benzoquinone ring was oriented as in **6**. Longithorone G (**7**) was found to differ from **6** in stereochemistry at C-2′, C-3′, and C-10′. The NOESY spectrum of **7** showed correlations between the aldehyde proton (H-13′) and H-5 and H-2′, indicating that these protons are all on the same face of the molecule. In contrast, no NOE was observed between the aldehyde proton (H-13′) and H-5 or H-2′ in

Table 4. NMR Data for Longithorone F (6)[a]

position	^{13}C (mult)[b]	^1H (mult, *J* in Hz)[c]	HMBC (C no.)	NOE correlations[d]
1*β*	29.2 (t)	3.35 (dd, 6.9, 12.2)	2, 3, 18, 19, 20	1α, 2
1α		2.93 (dd, 9.5, 12.2)	2, 3, 19	1*β*, 13, 18
2	123.9 (d)	5.31 (m)	1, 3, 13	1*β*, 4b
3	136.9 (s)			
4a[e]	39.0 (t)	2.14 (m)	6	4′a, 4b, 13
4b[e]		1.66 (m)		4a, 2, 13′
5	36.8 (d)	2.18 (m)	6, 7	6
6	121.8 (d)	4.89 (br s)	3′, 4, 5, 8, 14	5, 8b, 13
7	138.1 (s)			
8	36.1 (t)	1.70 (m)		6, 21
9a	26.0 (t)	1.98 (m)		
9b		1.54 (m)		12α
10	127.2 (d)	5.31 (m)		15
11	130.9 (s)			
12α	31.7 (t)	3.47 (br d, 19.4)	10, 11, 15, 16, 17, 21	12*β*, 9b, 8a
12*β*		2.73 (dd, 19.4, 2.6)	10, 11, 15, 17, 21	12α, 15
13	15.4 (q)	1.56 (s)	2, 3, 4	1α, 4a, 6, 18
14a	37.4 (t)	2.37 (br d, 15.5)	7	1′*β*, 14b
14b		2.10 (m)	8	14a
15	26.2 (q)	1.84 (s)	10, 11, 12	10, 12*β*, 21
16	146.9 (s)			
17	187.4 (s)			
18	129.5 (d)	6.48 (br s)	1, 17, 20	1α, 13
19	148.0 (s)			
20	188.1 (s)			
21	132.5 (d)	6.54 (dd, 2.3, 1.7)	12	8b, 15
1′α	28.3 (t)	3.20 (dd, 15.1, 6.9)	2′, 3′, 17′, 18′, 19′	1′*β*, 4′b
1′*β*		1.78 (m)		1′α, 2′, 19′
2′	44.7 (d)	2.10 (m)	3′, 18′	1′*β*, 5′b, 19′
3′	52.5 (s)			
4′a	30.1 (t)	1.77 (m)		4a
4′b		1.52 (m)		1′α
5′	19.7 (t)	1.52 (m)		2′, 6′
6′	129.2 (d)	4.83 (br d, 8.2)	8′	4′b, 8′b
7′	135.1 (s)			
8′a	39.9 (t)	2.13 (m)		8′b, 14′
8′b		1.94 (m)		6′, 8′a, 10′, 14′
9′	32.1 (t)	1.92 (m)		12′a, 21′
10′	43.2 (d)	3.47 (dd, 9.0, 3.6)	8′, 9′, 16′, 17′	8′b, 15′
11′	147.8 (s)			
12′a	110.9 (t)	4.85 (br s)	11′, 15′	9′, 10′, 12′b
12′b		4.74 (br s)	11′, 15′	15′
13′	206.3 (d)	9.65 (s)	3′	4b
14′	15.7 (q)	1.23 (s)	6′, 7′, 8′	8′, 21′
15′	21.4 (q)	1.64 (s)	10′, 11′, 12′	10′, 12′b, 21′
16′	151.5 (s)			
17′	186.1 (s)			
18′	152.2 (s)			
19′	133.8 (d)	6.53 (t, 2.3)	1′, 17′, 21′	1′*β*, 2′
20′	188.5 (s)			
21′	129.9 (d)	6.39 (d, 2.3)	10′, 17′, 19′	9′, 14′, 15′

[a] Spectra were recorded in $CDCl_3$. [b] ^{13}C NMR at 125 MHz, referenced to $CDCl_3$ (*δ* 77), multiplicities determined by DEPT experiment. [c] ^1H NMR at 500 MHz, referenced to residual solvent $CDCl_3$ (*δ* 7.26). [d] Data obtained from NOESY experiment with mixing time = 0.5 s. [e] The letters a and b designate different protons where the relative stereochemistry could not be assigned.

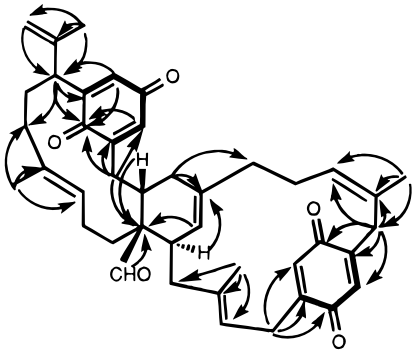
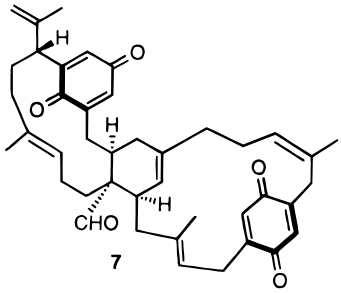


Figure 4. Correlations observed in the HMBC spectrum of longithorone F (**6**).

the spectra of **1**, **5**, or **6**. Prominent NOE correlations between H-19′ and H-2′ establish that C-19′ is directed below the plane of the drawing and toward H-1′. Furthermore, NOE correlation between H-21′ and H-15′ indicate that the isopropenyl group is directed behind the plane of the page and toward H-21′ to give the configuration shown at C-10′.



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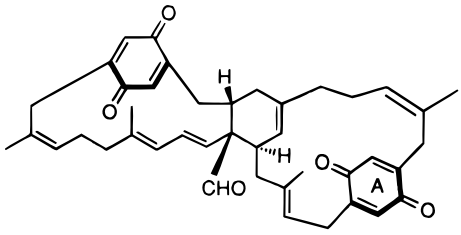


8

Longithorone H (**8**), $C_{42}H_{46}O_5$ by high resolution EIMS, was obtained as an amorphous powder, $[\alpha]_D = -51.0°$ (*c* 0.20, $CHCl_3$). The presence of 1,4 benzoquinones and conjugated double bonds were indicated by UV absorptions at 260 and 240 nm, and IR bands at 1648 and 1605 cm^{-1}. Five oxygens in the molecular formula were accounted for by two 1,4-benzoquinones (carbonyl resonances at δ 188.0, 187.7, 187.6, and 187.2) and an aldehyde group (IR absorption at 1717 cm^{-1}, a ^1H NMR singlet at δ 9.47, and a ^{13}C resonance at δ 206.0). Since no coupling was observed between the protons on the 1,4-benzoquinone rings, *para*-substitution was confirmed for these two rings. Due to the small amount isolated and problems with decomposition, only weak ^{13}C NMR data (see Experimental Section) were obtained for **8**, but interpretation of the COSY, LR-COSY, RCT-COSY, and NOESY spectra of **8** and comparison of its NMR data with that of the other longithorones led to formulation of structure **8** for longithorone H. Although HMBC data could not be obtained to provide evidence for connecting the smaller molecular segments deduced from vicinal couplings, long range H−H couplings summarized in Figure 6 verified many of the connectivities between protonated carbons and quaternary centers. The spin systems for the right hand macrocycle and the central

Table 5. NMR Data for Longithorone G (7)[a]

position	^{13}C (mult)[b]	^1H (mult, *J* in Hz)[c]	HMBC (C no.)	NOE correlations[d]
1β	29.0 (t)	3.29 (dd, 6.2, 12.0)	2, 3, 18, 19	1α, 2
1α		2.58 (dd, 10.0, 12.0)	2, 3, 18, 19, 20	1β, 13, 18
2	122.9 (d)	5.31 (dd, 10.0, 6.2)	1, 13	1β, 4b
3	136.0 (s)			
4a[e]	42.5 (t)	2.00 (dd, 15.5, 4.2)	3	4b, 5, 13
4b[e]		1.64 (m)	2, 3, 5, 13, 3′	2, 4a
5	37.3 (d)	2.34 (dt, 12.6, 4.3)		4a, 6, 13, 13′
6	122.0 (d)	4.77 (br d, 4.5)		5, 8a, 9, 13
7	137.6 (s)			
8a	35.0 (t)	1.66 (m)	6, 7	6, 8b
8b		1.50 (m)	6, 7	8a, 10
9	27.4 (t)	1.80 (m)	10, 11	6
10	126.4 (d)	5.08 (br d, 9.4)	12, 15	8, 15
11	131.7 (s)			
12α	33.1 (t)	3.48 (br d, 18.4)	10, 11, 16, 17, 21	12β
12β		2.45 (br d, 18.4)	11, 15, 16, 17	12α, 21
13	15.2 (q)	1.33 (s)	2, 3, 5	1α, 4a, 5, 6, 18
14a	37.8 (t)	1.76 (m)	7, 2′	
14b		1.66 (m)	6, 7	
15	27.1 (q)	1.68 (s)	10, 11, 12	10, 21
16	148.3 (s)			
17	187.9 (s)			
18	129.8 (d)	6.34 (s)	1, 19, 20	1α, 13
19	148.1 (s)			
20	187.0 (s)			
21	132.5 (d)	6.44 (t, 1.6)	12, 16, 17	12β, 15
1′β	28.7 (t)	3.51 (dd, 15.2, 8.0)	2′, 18′, 19′	1′α, 4′b
1′α		1.55 (m)	14, 3′, 17′, 18′, 19′	1′β, 19′
2′	39.1 (d)	1.76 (m)		19′
3′	53.7 (s)			
4′	33.1 (t)	1.31 (m)		1′β, 6′
5′a	22.4 (t)	1.75 (m)		14′
5′b		1.61 (m)		6′
6′	130.6 (d)	4.86 (t, 6.0)		4′b, 5′b, 8′b
7′	134.6 (s)			
8′a	39.8 (t)	1.90 (m)		
8′b		1.82 (m)		6′, 10′
9′a	31.4 (t)	1.65 (m)		
9′b		1.57 (m)		10′, 12′a
10′	43.3 (d)	3.60 (br d, 8.7)	9′, 11′, 12′, 16′, 17′, 21′	8′b, 9′b, 12′a
11′	147.0 (s)			
12′a	111.3 (t)	4.94 (br s)	10′, 11′, 15′	9′b, 10′, 12′b
12′b		4.80 (br s)	10′, 15′	12′a, 15′
13′	203.8 (d)	9.41 (s)		5, 2′, 4′, 5′a
14′	14.8 (q)	1.10 (s)	6′, 7′, 8′	5′a, 21′
15′	21.2 (q)	1.63 (s)	10′, 11′, 12′	12′b, 21′
16′	151.8 (s)			
17′	187.4 (s)			
18′	152.5 (s)			
19′	131.8 (d)	6.25 (dd, 2.6, 1.9)	1′, 17′, 21′	1′α, 2′
20′	187.6 (s)			
21′	130.9 (d)	6.48 (d, 2.6)	10′, 17′, 19′	14′, 15′

[a] Spectra were recorded in C_6D_6. [b] ^{13}C NMR at 125 MHz, referenced to C_6D_6 (δ 128), multiplicities determined by DEPT experiment. [c] ^1H NMR at 500 MHz, referenced to residual solvent C_6D_6 (δ 7.20). [d] Data obtained from NOESY experiment with mixing time = 0.5 s. [e] The letters a and b designate different protons where the relative stereochemistry could not be assigned.

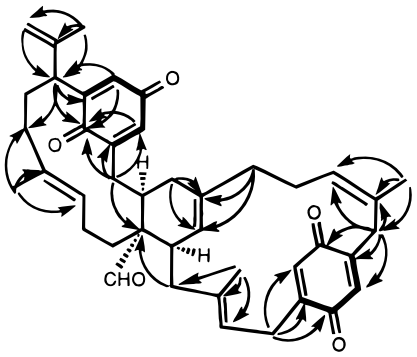


Figure 5. Correlations observed in the HMBC spectrum of longithorone G (**7**).

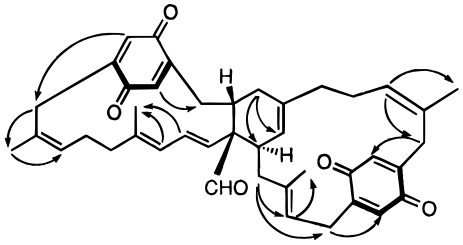


Figure 6. Selected long-range $^1H-^1H$ couplings from LR-COSY and RCT-COSY spectra of **8**.

six-membered ring were the same as for **1** and **5.** The orientation of the right hand benzoquinone ring was confirmed to be the same as in **1** and **5** by observation of NOE interactions between H-1β/H-18 and H-13/H-5 (no H-13/H-18 interaction) (Table 6). The double bond configurations 2*E*,10*Z* followed from NOE data (Table 6).

Assembly of the left hand macrocycle of **8** followed from observation of long range coupling from one of the benzoquinone protons (H-18′) to the H-1′s which in turn were coupled to H-2′ on the central six-membered ring. The other benzoquinone proton (H-21′) was long range coupled to H-12′s, and these were coupled to the vinyl methyl group (H-15′) which was further long range coupled to H-10′ as shown in Figure 6. The final segment of the left hand macrocycle, C-4′-C-7′ with branching C-14′ methyl was evident from vicinal couplings in the sequence H-4′ to H-6′, and allylic coupling of H-6′ to H-14′. Linkage of C-4′ to C-3′ was substantiated by two NOE correlations: H-5/H-5′ and H-4′/H-13′. Finally C-7′ must be connected to C-8′ to form a ring which accounts for the last degree of unsaturation. The double bond configurations were assigned as 4′*E* ($J_{4',5'}$ = 16 Hz), 6′*E* (NOE between H-5′/H-14′), and 10′*Z* (NOE between H-10′/H-15′). The assigned orientation of the left-hand benzoquinone ring is based on observation of NOE correlations between H-18′ and H-1′β, H-2′ and H-4′. Examination of models indicate that with the alternate orientation of the benzoquinone ring, H-18′ would be quite remote from H-2′.

Longithorone I (**9**), a minor metabolite having the formula $C_{42}H_{48}C_5$, was determined to be the 4′,5′-dihydro analog of **8** from detailed analysis of ^1H NMR data which led to the assignments in Table 6. Most of the proton NMR spin systems were the same as in the spectrum of **8**, and NOE's and long range couplings supporting the connection of the various structural units were the same except for the conjugated diene system. In place of the conjugated protons of **8**, the $=CHCH_2CH_2$ unit assigned to C-6′ to C-4′ was ascertained from COSY, LR-COSY,

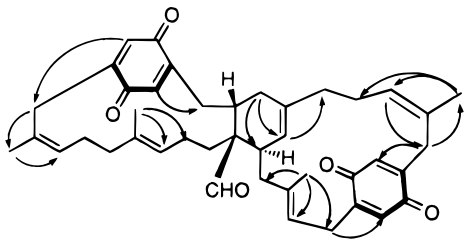
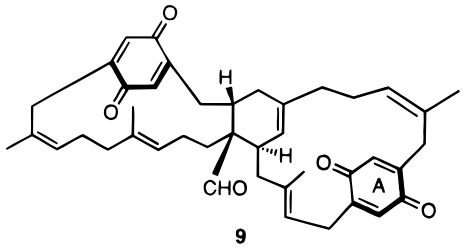


Figure 7. Selected long-range $^1H-^1H$ couplings from LR-COSY and RCT-COSY spectra of **9**.

and RCT-COSY spectra. NOE correlations around the double bonds and both benzoquinone rings was the same for **9** as **8** (Table 6), and hence the two compounds are assigned the same configurations.



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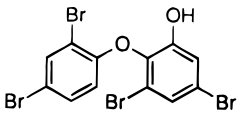

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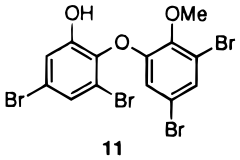

11

The longithorones possess unprecendented carbocyclic skeletons derived formally by cyclization of farnesyl hydroquinone to give [9]- and [10]metacyclophane and [12]paracyclophane structures. Although compounds of mixed biogenesis featuring the farnesyl (or cyclized farnesyl) hydroquinone skeleton are well-known,[2,16] cyclization of the farnesyl chain with the hydroquinone unit to give a macrocycle is rare, one example being the smenochromenes[16] which feature ortho-bridging of a hydroquinone by the termini of a farnesyl unit. As mentioned in our earlier paper,[9] we speculate that the dimeric longithorones may arise by Diels–Alder reactions of suitably unsaturated precursors such as are depicted in Scheme 1. The discovery of monomers **2**–**4** supports this suggestion. The stereochemistry of the central carbocyclic rings in **1** and **5**–**9** is consistent with Diels–Alder reactions. An intermolecular Diels–Alder reaction has been proposed as a step in the biogenesis of the tetraterpenoid methyl isotortuate,[17] and intramolecular "4 + 2" cycloadditions have been invoked to explain the formation of various complex alkaloids, e.g. the manzamines,[18] xestocyclamine,[19] the ingenamines,[20] and mandangamine.[21]

Scheme 1

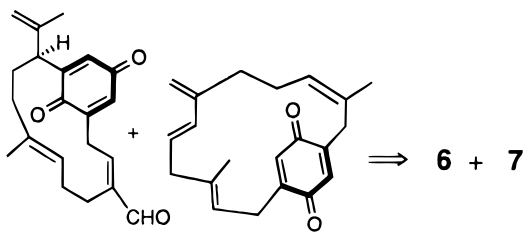

Table 6. NMR Data for Longithorones H (8) and I (9)[a]

	longithorone H			longithorone I	
position	^{1}H (C_6D_6)	^{1}H ($CDCl_3$)	NOE correlations[b]	^{1}H (C_6D_6)	NOE correlations
1α	3.76 (t, 11.7)	3.82 (t, 11.5)	1*β*, 13	3.74 (t, 11.3)	1*β*, 13
1*β*	2.17 (dd, 11.7, 5.4)	2.65 (dd, 11.5, 4.7)	1α, 2, 4b, 18	2.18 (dd, 11.3, 5.2)	1α, 2, 18
2	4.70 (dd, 11.7, 5.4)	4.96 (dd, 11.5, 4.7)	1*β*, 4b	4.69 (dd, 11.3, 5.2)	1*β*, 4b
4a[c]	2.49 (br d, 11.2)	2.41 (m)	4b, 5′, 13	2.29 (br d, 11.0)	4b
4b[c]	1.96 (m)	1.92 (m)	1*β*, 2, 4a, 13′	1.80 (m)	2, 4a, 13′
5	3.11 (br d, 12.7)	2.84 (br d, 13.1)	1′α, 5′, 6, 13	2.57 (m)	6
6	5.19 (br s)	5.06 (br s)	5	5.06 (br s)	5, 9a, 9b
8	1.72 (m)	1.76 (m)	10	1.70 (m)	10
9a	2.15 (m)	2.11 (m)	9b, 10	2.08 (m)	6
9b	1.83 (m)	1.87 (m)	9a, 12*β*	1.74 (m)	6
10	5.13 (m)	5.09 (m)	8, 9a, 15	5.11 (m)	8, 15
12*β*	3.02 (dd, 16.1, 2.0)	3.22 (dd, 16.4, 1.8)	9b, 12α	3.06 (br d, 16.5)	12α, 15
12α	2.56 (dd, 16.1, 2.0)	3.01 (br d, 16.4)	12*β*, 21	2.55 (br d, 16.5)	12*β*, 21
13	2.13 (s)	1.90 (s)	1α, 4a, 5	1.92 (s)	1α
14a	2.36 (m)	1.80 (m)		2.55 (m)	13′, 14b
14b	1.46 (m)	1.74 (m)	2′	1.47 (m)	14a
15	1.92 (s)	1.87 (s)	10	1.88 (s)	10, 12*β*
18	6.16 (br s)	6.59 (s)	1*β*	6.25 (s)	1*β*
21	6.24 (br s)	6.75 (d, 1.5)	12α	6.23 (d, 1.2)	12α
1′α	3.17 (t, 13.2)	3.08 (dd, 11.7, 14.2)	1′*β*, 5	3.13 (dd, 10.7, 15.0)	1′*β*
1′*β*	1.40 (m)	1.82 (m)	1′α, 18′	1.47 (m)	1′α, 18′
2′	2.26 (m)	2.38 (m)	13′, 14b, 18′	2.39 (m)	18′
4′	5.10 (d, 16.1)	5.03 (d, 16.1)	6′, 13′, 18′	0.80 (m)	5′
5′	6.06 (dd, 16.1, 10.7)	5.90 (dd, 16.1, 10.9)	4a, 5, 14′	1.79 (m)	4′, 6′, 14′
6′	5.34 (br d, 10.7)	5.57 (br d, 10.9)	4′	4.61 (br t)	5′, 8′
8′	1.78 (m)	1.84 (m)	10′	1.90 (m)	6′
9′a	1.89 (m)	2.23 (m)		2.00 (m)	
9′b	1.59 (m)	2.02 (m)	12′*β*	2.00 (m)	
10′	5.14 (m)	5.41 (dd, 10.2, 5.7)	8′, 15′	5.13 (m)	15′
12′*β*	3.44 (br d, 18.6)	3.41 (br d, 18.9)	9′b, 12′α	3.16 (dd, 15.4, 1.5)	12′α, 15′
12′α	2.46 (dd, 18.6, 2.0)	2.61 (dd, 18.9, 2.2)	12′*β*	2.44 (br d, 15.4)	12′*β*, 21′
13′	9.53 (s)	9.47 (s)	2′, 4b, 4′	9.46 (s)	4b, 14a
14′	1.58 (s)	1.68 (s)	21′	1.44 (s)	5′
15′	1.62 (s)	1.81 (s)	10′, 21′	1.92 (s)	10′, 12′*β*
18′	6.24 (br s)	6.47 (d, 1.5)	1′*β*, 2′, 4′	6.38 (d, 2.1)	1′*β*, 2′
21′	6.16 (br s)	6.28 (t, 2.0)	14′, 15′	6.35 (d, 1.2)	12′α

[a] ^{1}H NMR at 500 MHz, referenced to residue solvent C_6D_6 (δ 7.20), $CDCl_3$ (δ 7.26). [b] NOESY experiment recorded in $CDCl_3$ with mixing time = 0.5 s. [c] The letters a and b designate different protons where the relative stereochemistry could not be assigned.

Experimental Section

General Procedures. UV and IR spectra were recorded on a Bio-Rad 3240-spc FT and a Hewlet Packard spectrophotometer, respectively. Optical rotations were measured on a Rudolph Autopol III polarimeter (*c* g/100 mL) at 589 nm. High resolution fast atom bombardment mass spectra (HRFABMS) were recorded in a 3NBA matrix in the positive ion mode on a VG-ZAB-E mass spectrometer. High resolution electron-impact mass spectra (HREIMS) were measured on a 70-VSE instrument. HPLC was conducted using a UV detector (260 nm) and Phenosphere 5 ODS 3 (250 × 10.0 mm), Whatman Partisil M 20 (250 × 20.0 mm), and Spherex 5 SiO_2 (300 × 10.0 mm) columns. NMR experiments were performed on Varian XL-300 and VXR-500 instruments; signals are reported in parts per million (δ), referenced to the solvents used. All NMR pulse sequences were run using standard Varian software, version 4.3. The NOESY experiments were acquired in the phase-sensitive mode with relaxation delay 2 s, mixing time 500 ms.

Isolation. The tunicate *A. longithorax* (reference number 4PA93, 1PA94, and OCDN 1052C) was collected in Palau and identified by Dr. F. Monniot, Museum National d'Histoire Naturelle, Paris, France. Freshly thawed specimens of *A. longithorax* (7.9 kg wet wt; 218 g dry wt after extraction) were extracted with MeOH (3 × 10 L), and then with MeOH/CH_2Cl_2 (1:1, 3 × 8 L). All extracts were combined and the solvents[19] evaporated. The residue was dissolved in 10% aqueous MeOH (3 L), and the solution extracted with hexane (3 × 3 L) to yield, after evaporation of solvent, 5 g of hexane extract. The aqueous MeOH solution was diluted with H_2O (~860 mL) to 30% H_2O in MeOH and extracted with CH_2Cl_2 (3 × 1.8 L), to give 10 g of CH_2Cl_2-solubles. The aqueous MeOH phase was concentrated *in vacuo* and the aqueous concentrate extracted with n-BuOH (3 × 1 L). The hexane solubles were subjected to chromatography over silica gel using increasing amounts of EtOAc in hexane as eluent (5% EtOAc in hexane to 100% EtOAc). Twelve fractions were collected.

The least polar fraction (5% EtOAc in hexane eluate) which contained primarily long chain methyl esters with minor amounts of a quinone mixture and a glycerol ether was fractionated on a SiO_2 column using hexane/CH_2Cl_2 gradient elution. The mixture of quinone compounds (20% CH_2Cl_2 in hexane) therefrom was further separated by reversed phase HPLC (Phenosphere 5 ODS_3) using CH_3CN as eluent to afford, in order of increasing retention time, longithorone B (**2**) (11.0 mg), longithorone C (**3**) (0.8 mg), and longithorone D (**4**) (3.8 mg).

The sixth fraction (15% EtOAc in hexane eluate) which contained a terpenoid mixture and some sterols was passed over a silica gel Sep-Pak (eluted by CH_2Cl_2) and then a SiO_2 HPLC column (Whatman Partisil M 20) using 5% acetone in CH_2Cl_2 as eluent to remove the sterols. The major fraction therefrom was further fractionated by HPLC on a silica gel column (Spherex 5 SiO_2) using acetone/CH_2Cl_2 (1:80) as eluent to yield longithorone A (**1**) and a mixture which contained

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mostly compounds **5** and **6** but also minor amounts of quinones **7**−**9**. This mixture was resolved by repeated reversed phase HPLC on a Phenosphere 5 ODS 3 column using 10% H_2O in CH_3CN as eluent to furnish longithorones E (**5**), F (**6**), G (**7**), H (**8**), and I (**9**). More of the compounds were obtained from the fourth and fifth fractions of the original silica gel chromatography using the same reversed phase HPLC protocol. Due to the problems with decomposition of the pure compounds, only small amounts of pure compounds were isolated at any given time. From the various amounts isolated, the percent yields of each compound are estimated to be as follows: **1** (2.5 × 10^{-2}% of dry specimens), **2** (5.0 × 10^{-3}%), **3** (3.7 × 10^{-4}%), **4** (1.7 × 10^{-3}%), **5** (1.2 × 10^{-2}%), **6** (1.0 × 10^{-2}%), **7** (5.5 × 10^{-3}%), **8** (2.5 × 10^{-3}%), and **9** (1.3 × 10^{-3}%). Freshly purified samples were used for measurement of physical constants and spectral data.

Longithorone A (1): NMR data in C_6D_6 (position, δC/δH) C-1, 27.6 (t)/3.72 (t, 11.7), 2.17 (dd, 11.7, 4.9); C-2, 125.3 (d)/4.70 (dd, 11.7, 4.9); C-3, 136.3 (s); C-4, 40.5 (t)/2.25 (br d, 11.2), 1.75 (m); C-5, 36.3 (d)/3.20 (br d, 12.2); C-6, 119.7 (d)/5.09 (br s); C-7, 134.7 (s); C-8, 37.4 (t)/1.65 (m); C-9, 26.6 (t)/2.08 (m), 1.78 (m); C-10, 126.6 (d)/5.09 (m); C-11, 132.5 (s); C-12, 35.6 (t)/3.02 (dd, 16.1, 1.5), 2.50 (br d, 16.1); C-13, 15.3 (q)/2.09 (s); C-14, 32.9 (t)/2.12 (m), 1.21 (br d, 18.5); C-15, 27.6 (q)/1.83 (s); C-16, 149.4 (s); C-17, 187.2 (s); C-18, 131.5 (d)/6.23 (br s); C-19, 148.1 (s); C-20, 187.0 (s); C-21, 133.6 (d)/6.25 (br s); C-1′, 37.8 (t)/1.87 (m), 1.04 (m); C-2′, 30.7 (d)/1.92 (m); C-3′, 49.4 (s); C-4′, 27.6 (t)/2.46 (dd, 13.7, 4.4), 1.75 (m); C-5′, 38.1 (d)/1.90 (m); C-6′, 126.1 (d)/5.01 (br s); C-7′, 143.8 (s); C-8′, 34.3 (t)/1.88 (m), 1.65 (m); C-9′, 29.9 (t)/1.88 (m), 1.68 (m); C-10′, 130.4 (d)/5.06 (m); C-11′, 132.2 (s); C-12′, 34.5 (t)/2.81 (dd, 14.2, 2.0), 2.43 (br d, 14.2); C-13′, 205.5 (d)/9.70 (s); C-14′, 30.9 (t)/2.00 (m); C-15′, 27.5 (q)/1.80 (s); C-16′, 155.7 (s); C-17′, 200.7 (s); C-18′, 56.3 (d)/2.65 (dd, 8.8, 1.9); C-19′, 52.9 (s); C-20′, 201.2 (s); C-21′, 139.2 (d)/5.98 (d, 1.5).

Longithorone B (2): $[\alpha]_D$ = −92.4° (*c* 0.57, CH_2Cl_2); mp 80−82 °C (MeOH/CH_2Cl_2); UV (EtOH) λ_{max} 258 (ε 14228) nm; IR (neat) ν_{max} 1649 (vs), 1610, 1440, 1250 cm^{-1}; HREIMS *m*/*z* 310.1924 $[M]^+$ ($C_{21}H_{26}O_2$, Δ = 0.8 mmu); ^1H and ^{13}C NMR see Table 1.

Longithorone C (3): $[\alpha]_D$ = −15.0° (*c* 0.07, CH_2Cl_2); UV (EtOH) λ_{max} 260 (ε 15125) nm; IR (neat) ν_{max} 1648 (vs), 1605, 1405, 1245 cm^{-1}; EIMS (70 eV) *m*/*z* 310 $[M]^+$; ^1H and ^{13}C NMR see Table 1.

Longithorone D (4): $[\alpha]_D$ = −305.3° (*c* 0.23, CH_2Cl_2); mp 127−129 °C (MeOH/CH_2Cl_2); UV (EtOH) λ_{max} 256 (ε 10370) nm; IR (neat) ν_{max} 1655, 1600, 1440, 1290 cm^{-1}; HREIMS *m*/*z* 310.1925 $[M]^+$ ($C_{21}H_{26}O_2$, Δ = 0.8 mmu); ^1H and ^{13}C NMR see Table 2.

Longithorone E (5): $[\alpha]_D$ = −35.4° (*c* 0.48, $CHCl_3$); mp > 230 °C dec; UV (EtOH) λ_{max} 258 (ε 23920) nm; IR (neat) ν_{max} 1714, 1654, 1602, 1443, 1260, 1122 cm^{-1}; FABMS *m*/*z* 633 $[M + 1]^+$, 634 $[M + 2]^+$, 635 $[M + 3]^+$; HRFABMS *m*/*z* 633.3616 $[M + 1]^+$ ($C_{42}H_{49}O_5$, Δ = −3.6 mmu), 634.3647 $[M + 2]^+$ ($C_{42}H_{50}O_5$, Δ = 1.1 mmu); EIMS (12 eV) *m*/*z* 636 (2.4) $[M + 4]^+$, 634 (3.6) $[M + 2]^+$, 326 (23.8), 324 (100, 310 (35.7), 308 (15.7); ^1H and ^{13}C NMR measured in C_6D_6 see Table 3. ^1H NMR (300 MHz, $CDCl_3$), 9.54 (s) (H-13′), 6.68 (br s, H-21), 6.63 (dd, *J* = 2.4, 2.0 Hz, H-19′), 6.57 (br s, H-18), 6.42 (d, *J* = 2.4 Hz, H-21′), 5.10 (m, H-10), 4.96 (br s; H-12′), 4.93 (m, H-2), 4.86 (br s, H-12′), 4.78 (br s, H-5), 4.74 (br d, *J* = 8.1 Hz, H-6′), 3.78 (t, *J* = 11.2 Hz, H-1), 3.45 (br d, *J* = 9.8 Hz, H-10′), 3.23 (br d, *J* = 16.6 Hz, H-12), 3.01 (dd, *J*= 15.0, 6.5 Hz, H-1′), 2.97 (br d, *J* = 16.6 Hz, H-12), 2.65 (m, H-1), 2.58 (m), 2.47 (m), 2.40 (m), 2.25 (m), 2.14 (m), 1.86 (s), 1.81 (s), 1.65 (s), 1.21 (s), 1.08 (m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.42 (q), 15.46 (q), 20.74 (t), 21.52 (q), 26.50 (t), 27.20 (q), 27.90 (t), 29.42 (t), 30.54 (t), 32.24 (t), 35.18 (t), 36.97 (t), 37.04 (d), 37.55 (t), 39.12 (d), 39.92 (t), 40.10 (t), 43.25 (d), 52.82 (s), 110.87 (t), 120.47 (d), 125.46 (d), 126.56 (d), 130.10 (d), 130.35 (d), 131.60 (d), 131.73 (s), 133.44 (d), 133.65 (d), 134.55 (s), 135.36 (s), 136.02 (s), 147.05 (s), 148.09 (s), 149.60 (s), 151.53 (s), 152.43 (s), 186.49 (s), 187.34 (s), 187.46 (s), 187.55 (s), 205.51 (d).

Longithorone F (6): $[\alpha]_D$ = −65.2° (*c* 0.89, $CHCl_3$); UV (EtOH) λ_{max} 258 (ε 24940) nm; IR (neat) ν_{max} 1716, 1650, 1608, 1445, 1290, 1255 cm^{-1}; HRFABMS *m*/*z* 633.3629 $[M + 1]^+$ ($C_{42}H_{39}O_5$, Δ = −4.9 mmu), 634.3654 $[M + 2]^+$ ($C_{42}H_{50}O_5$, Δ = 0.4 mmu), 635.3768 $[M + 3]^+$ ($C_{42}H_{51}O_5$, Δ = −3.1 mmu), 636.3817 $[M + 4]^+$ ($C_{42}H_{52}O_5$, Δ = −0.2 mmu); EIMS (12 eV) *m*/*z* 636 (3.4) $[M + 4]^+$, 634 (7.6) $[M + 2]^+$, 632 (4.8) $[M]^+$, 619 (2.5), 616 (3.6), 608 (49), 606 (8.0), 604 (5.0), 326 (23.7), 324 (100), 310 (31), 308 (25.3). ^1H and ^{13}C NMR measured in $CDCl_3$ see Table 4. NMR data in C_6D_6 (position, δC/δH) C-1, 29.4 (t)/3.32 (dd, 11.9, 6.1), 2.57 (dd, 11.9, 9.8); C-2, 124.3 (d)/5.40 (dd, 9.8, 6.1); C-3, 136.9 (s); C-4, 39.2 (t)/1.86 (m), 1.46 (br d, 11.3); C-5, 36.9 (d)/1.79 (m); C-6, 121.7 (d)/4.90 (br s); C-7, 138.1 (s); C-8, 36.2 (t)/1.87 (m), 1.70 (m); C-9, 26.4 (t)/1.87 (m), 1.57 (m); C-10, 127.2 (d)/5.22 (m); C-11, 131.5 (s); C-12, 31.8 (t)/3.58 (br d, 19.3), 2.52 (dd, 19.3, 2.4); C-13, 15.1 (q)/1.22 (s); C-14, 37.5 (t)/1.84 (m), 1.78 (m); C-15, 26.4 (q)/1.65 (s); C-16, 147.3 (s); C-17, 187.1 (s); C-18, 129.7 (d)/6.28 (br s); C-19, 148.0 (s); C-20, 187.8 (s); C-21, 132.8 (d)/6.51 (dd, 2.2, 1.5); C-1′, 28.5 (t)/3.37 (dd, 15.0, 7.4), 1.42 (br d, 15.0); C-2′, 44.6 (d)/1.67 (m); C-3′, 52.5 (s); C-4′, 30.4 (t)/1.68 (m); C-5′, 19.9 (t)/1.48 (m), 1.35 (m); C-6′, 129.7 (d)/4.75 (br d, 7.7); C-7′, 134.7 (s); C-8′, 40.1 (t)/1.86 (m), 1.78 (m); C-9′, 32.2 (t)/1.66 (m); C-10′, 43.5 (t)/3.60 (dd, 10, 2.7); C-11′, 147.8 (s); C-12′, 111.2 (t)/4.95 (br s), 4.79 (br s); C-13′, 205.1 (d)/9.52 (s); C-14′, 15.6 (q)/1.12 (s); C-15′, 21.3 (q)/1.64 (s); C-16′, 151.4 (s); C-17′, 186.2 (s); C-18′, 152.1 (s); C-19′, 134.1 (d)/6.30 (dd, 2.4 1.8); C-20′, 188.1 (s); C-21′, 130.2 (d)/6.45 (d, 2.4).

Longithorone G (7): $[\alpha]_D$ = +73.5° (*c* 0.34, $CHCl_3$); UV (EtOH) λmax 258 (ε 25698) nm; IR (neat) ν_{max} 1717, 1654, 1605, 1445, 1260, 1120 cm^{-1}; HRFABMS *m*/*z* 634.3681 $[M + 2]^+$ ($C_{42}H_{50}O_5$, Δ = 2.3 mmu), 635.3744 $[M + 3]^+$ ($C_{42}H_{51}O_5$, Δ = 0.7 mmu); EIMS (12 eV) *m*/*z* 634 (4.6) $[M + 2]^+$, 326 (43.6), 324 (100), 310 (25.5), 308 (23.9); ^1H and ^{13}C NMR see Table 5.

Longithorone H (8): $[\alpha]_D$ = −51.0° (*c* 0.20, $CHCl_3$); UV ($CHCl_3$) λ_{max} ~240 (ε 11340), 260 (ε 15360) nm; IR (neat) ν_{max} 1717, 1648, 1605, 1438, 1260, 1115 cm^{-1}; HREIMS *m*/*z* 632.3498 $[M + 2]^+$ ($C_{42}H_{48}O_5$, Δ = 0.4 mmu); EIMS (70 eV) *m*/*z* 632 (39) $[M^+ + 2]$, 324 (100), 322 (30), 310 (52), 308 (35); ^1H NMR see Table 6; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.0, 188.0, 187.7, 187.6, 187.2, 150.6, 149.7, 148.2, 148.1, 140.8, 136.0, 135.4, 133.6, 133.2, 131.9, 131.6, 131.5, 130.7, 129.9, 192.5, 129.0, 126.4, 126.3, 125.5, 119.3, 55.9, 43.9, 39.7, 37.4, 37.2, 35.6, 35.4, 31.6, 30.5, 29.7, 29.1, 27.8, 27.3, 26.3, 25.3, 18.7, 15.1.

Longithorone I (9): $[\alpha]_D$ = −49.5° (*c* 0.07, CH_2Cl_2); UV (EtOH) λ_{max} 256 (ε 10934) nm; IR (neat) ν_{max} 1709, 1650, 1606, 1447, 1295, 1255 cm^{-1}; HRFABMS *m*/*z* 633.3582 $[M + 1]^+$ ($C_{42}H_{49}O_5$, Δ = 0.2 mmu), 634.3672 $[M + 2]^+$ ($C_{42}H_{50}O_5$, Δ = 1.4 mmu), 635.3737 $[M + 3]^+$ ($C_{42}H_{51}O_5$, Δ = 1.5 mmu); ^1H NMR see Table 6.

3,5-Dibromo-2-(2′,4′-dibromophenoxy)phenol (10):[10b] mp 168−9 °C; ^1H NMR ($CDCl_3$) δ 7.76 (d, 2), 7.32 (d, 2), 7.27 (dd, 8, 2), 7.20 (d, 2), 6.42 (d, 8); ^{13}C NMR (acetone-d_6) δ 153.9, 153.0, 139.8, 136.3, 132.3, 126.9, 120.8, 119.8, 118.7, 116.8, 115.0, 112.9; ^{13}C NMR ($CDCl_3$) δ 152.0, 150.3, 138.6, 136.1, 131.5, 127.7, 119.8, 119.6, 117.2, 116.0, 115.9, 112.6.

3,5-Dibromo-2-(2′-methoxy-3′,5′-dibromophenoxy)phenol (11):[10a] ^1H NMR (CD_3OD) δ 7.37 (d, 2), 7.31 (d, 2), 7.12 (d, 2), 6.50 (d, 2), 3.98 (s); ^{13}C NMR (DMSO-d_6) δ 152.2, 151.1, 145.0, 137.7, 128.0, 124.8, 119.6, 118.9, 118.6, 118.0, 116.3, 116.1; 60.5; ^{13}C NMR ($CDCl_3$) δ 150.8, 150.7, 145.4, 138.4, 129.9, 127.0, 120.3, 119.8, 118.9, 117.8, 117.4, 117.3, 61.4.

Crystal Structure Determination of 2, 4, and 5. All the X-ray measurements were carried out on an Enraf-Nonius CAD-4 automatic diffractometer equipped with a liquid N_2 low-temperature device. All three structures were solved by the direct methods using the program SHELXS-86[22] and refined by a full-matrix least-squares routine[23] where the quantity $\Sigma\omega(F_o - F_c)^2$ was minimized. Compound **2** was crystallized from $CHCl_3$/MeOH as colorless blocks. The unit cell parameters

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were obtained from a least-squares fit to $\pm 2\theta$ values of 25 reflections measured at 188 K. Crystal data: $C_{21}H_{26}O_2$, FW = 310.4, monoclinic, $P2_1$, a = 15.218(8) Å, b = 6.577(3) Å, c = 9.548(5) Å, β = 103.16(5)°, V = 930.6(9) Å^3, Z = 2, λ = 0.71069 Å, μ(Mo Kα) = 0.4 cm^{-1}, D(calc) = 1.108 g/cm^3. Intensity data were measured at 188 K employing $\theta-2\theta$ scan technique. A total of 2089 reflections ($2\theta_{max}$ = 53°) were measured of which 1836 were considered observed ($I > 2\alpha(I)$). The non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms were located from a difference Fourier map and were refined isotropically. R = 5.10%, R_ω = 5.8%, S = 2.1, $\Delta\rho$(max) = 0.20 eÅ^{-3}, Δ/σ(max) = 0.01.

Compound **4** crystallized from MeOH−CH_2Cl_2 as colorless plates. The unit cell parameters were obtained from a least-squares fit to $\pm 2\theta$ values of 25 reflections measured at 188 K. Crystal data: $C_{21}H_{26}O_2$, FW = 310.4, orthorhombic, $P2_12_12_1$, a = 12.957(6) Å, b= 16.006(6) Å, c = 9.050(4) Å, V = 1876.8(8) Å^3, Z = 4, λ = 0.71069 Å, μ(Mo Kα) = 0.4 cm^{-1}, D(calc) = 1.098 g/cm^3. Intensity data were measured at 188 K employing $\theta-2\theta$ scan technique. A total of 2220 reflections ($2\theta_{max}$ = 53°) were measured of which 1150 were considered observed ($I > 2\sigma(I)$). The hydrogen atoms were located from a difference Fourier map, and they were refined with isotropic temperature factors. R = 5.2%, R_ω = 4.7%, S = 1.4, $\Delta\rho$(max) = 0.16 eÅ^{-3}, Δ/σ(max) = 0.01.

Compound **5** crystallized from CH_2Cl_2 as yellowish needles. The unit cell parameters were obtained from a least-squares fit to $\pm 2\theta$ values of 25 reflections measured at 188 K. Crystal data: $C_{42}H_{48}O_5 + CH_2Cl_2$, FW = 717.8, monoclinic, $P2_1$, a = 17.568(4) Å, b = 7.470(2) Å, c = 14.873(3) Å, β = 93.57(3)°, V = 1948.0(6) Å^3, Z = 2, λ = 1.54178 Å, μ(Cu Kα) = 17.3 cm^{-1}, D(calc) = 1.223 g/cm^3. Intensity data were measured using Cu Kα radiation at 188 K and employing $\theta-2\theta$ scan technique. A total of 4100 reflections ($2\theta_{max}$ = 150°) were measured of which only 2867 were considered observed ($I > 2\alpha(I)$). Several peaks in the difference Fourier map indicated the presence of disordered solvent which could not be resolved. Five fairly well resolved peaks were refined as oxygen atoms (one with half occupancy). This gave a reasonable convergence of least-squares refinement and a cleaner difference Fourier map. About half of the hydrogen atoms of **5** were located from difference Fourier maps, and the rest were placed in their calculated positions. All the hydrogen atoms were refined isotropically (using distant constraint routine DFIX in SHELX program). R = 6.4%, R_ω = 6.8%, S = 2.0, $\Delta\rho$(max) = 0.30 eÅ^{-3}, Δ/σ(max) = 0.10.

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Supporting Information Available: ^{1}H NMR spectra for longithorone A−I (**1**−**9**) and ^{13}C NMR spectra for longithorone A−H (**1**−**8**) (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(24) The authors have deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.