Total Synthesis, Absolute Configuration, and Later Isolation of (−)-Prehalenaquinone, a Putative Biosynthetic Precursor to the Marine Natural Products Halenaquinone and Xestoquinone

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As part of the total syntheses of halenaquinone (**1**) and xestoquinone (**4**), cardiotonic and cytotoxic marine natural products isolated from tropical marine sponges, we have found a new reaction pathway of the DMSO/DCC/PPTS or PTFA reagent that is useful for constructing a dihydrofuran ring system. By application of the reaction, we prepared synthetic intermediate (3*S*,3a*S*,12b*S*)-(−)-**8** with a dihydrofuran ring moiety, from which both (+)-halenaquinone (**1**) and (+)-xestoquinone (**4**) were synthesized; DMSO/DCC/PPTS oxidation of dihydrofuran-alcohol **8** led to **1**, while acid-catalyzed dehydration led to **4**. The mechanism of the new DMSO/ DCC/PPTS or PTFA reaction was clarified by use of ^{18}O labeling. We postulated that these synthetic routes might simulate the biosyntheses of **1** and **4** in marine sponges, and putative biosynthetic precursor (3*S*,3a*S*,12b*S*)-(−)-**7**, named prehalenaquinone, was synthesized. Later, we succeeded in isolating (−)-**7** from an Okinawan marine sponge, *Xestospongia sapra*.

Introduction

Marine sponges are one of the major natural sources of novel biologically active natural products. For example, a series of novel pentacyclic quinones and hydroquinones of the halenaquinol family have been isolated from tropical marine sponges. Halenaquinone (**1**), an antibiotic, was first isolated by Scheuer and coworkers from *Xestospongia exigua* collected in the Western Caroline Islands.[2] Halenaquinol (**2**) and its sulfate (**3**) were isolated from the Okinawan sponge *Xestospongia sapra* by Kitagawa and co-workers.[3] Xestoquinone (**4**), a less oxidized compound and a powerful cardiotonic constituent, was isolated by Nakamura and co-workers from the same Okinawan sponge, *Xestospongia sapra*.[4] Later, tetrahydroxestoquinol (**5**) and dihydrofuran compound **6** were isolated by Schmitz and his co-worker from a sponge, *Adocia sp.*, collected in the Truk Lagoon, together with halenaquinone (**1**) and xestoquinone (**4**).[5] Some of these compounds of the halenaquinol family showed cytotoxicity.[5,6] These biologically active natural products differ in oxidation state at the 3-, 8-, and 11-positions and also in the furan ring part. However, the relationships among these compounds, especially those among halenaquinone (**1**), xestoquinone (**4**), and dihydrofuran compound **6**, are still unclear.

The absolute stereochemistry of marine natural products **1**−**4** had already been determined by us in a nonempirical manner by the theoretical calculation of the CD spectra of naphthalenediene derivatives.[7,8] We had also proved that the absolute configurations theoretically determined were correct by achieving the first total syntheses[9] of (+)-halenaquinone (**1**), (+)-halenaquinol (**2**),[10] xestoquinol, and (+)-xestoquinone (**4**)[11,12] in natural enantiomeric forms. We recently obtained some interesting results on the relationships among halenaquinol compounds **1**, **4**, and **5**, and we report here the synthesis, absolute stereochemistry, and isolation of (−)-prehalenaquinone (**7**), a putative biosynthetic precursor common to halenaquinone and xestoquinone compounds.

The combination of DMSO/DCC/PPTS or PTFA has extensively been used as one of the most versatile oxidizing reagents for conversion of alcohols to aldehydes or ketones.[13] As part of the total syntheses of halenaquinone (**1**) and xestoquinone (**4**), however, we recently found a novel reaction between DMSO/DCC/PPTS or PTFA and alcohols: a substitution reaction useful for

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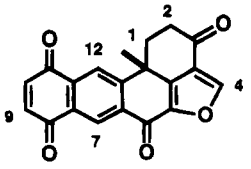
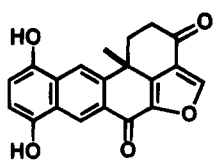
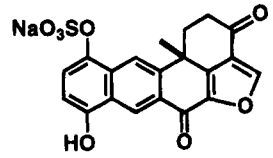
Chart 1



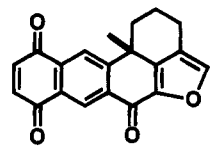
(12b*S*)-(+)-1



(12b*S*)-(+)-2



(12b*S*)-(+)-3



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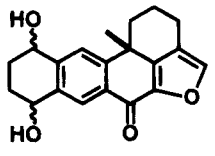
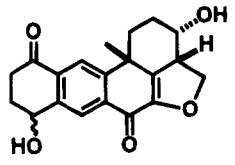
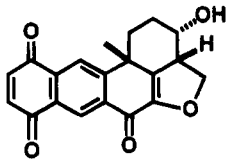


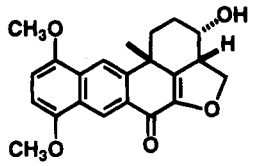
5



6



(3*S*,3a*S*,12b*S*)-(−)-7



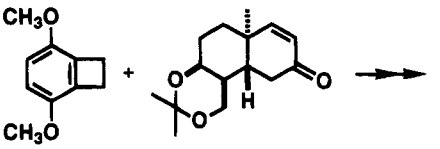
(3*S*,3a*S*,12b*S*)-(−)-8

constructing a dihydrofuran ring system. By application of the DMSO/DCC/PPTS reaction, we prepared key synthetic intermediate (3*S*,3a*S*,12b*S*)-(−)-**8** with a dihydrofuran ring moiety, which provided us with synthetic routes to (+)-halenaquinone (**1**) and to (+)-xestoquinone (**4**). The prolonged DMSO/DCC/PPTS oxidation reaction of dihydrofuran alcohol **8** yielded halenaquinol dimethyl ether (+)-**13**, which had previously been converted to (+)-**1**, and the acid-catalyzed dehydration of **8** afforded xestoquinol dimethyl ether, which was convertible to (+)-**4**. The mechanism of the new DMSO/DCC/PPTS or PTFA reaction was clarified by use of the ^{18}O-labeling method. We postulated that these synthetic routes might simulate the actual biosyntheses of **1** and **4** in marine sponges, and we synthesized the putative biosynthetic precursors, (3*S*,3a*S*,12b*S*)-(−)-**7** and its hydroquinone derivative. Later, we succeeded in isolating (−)-**7**, named prehalenaquinone, from an Okinawan marine sponge, *Xestospongia sapra*.

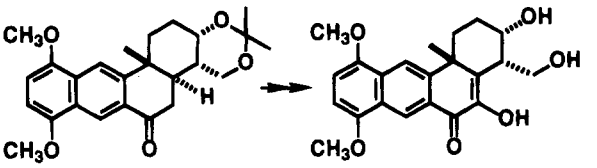
Results and Discussion

Dihydrofuran Ring Formation with DMSO/DCC/PPTS or PTFA. In our previous first total synthesis of (+)-halenaquinone (**1**) and (+)-halenaquinonol (**2**), we employed the strategy shown in Scheme 1.[10] The Diels-Alder reaction of 3,6-dimethoxybenzocyclobutene (**9**) and enone (4a*S*,7*S*,8*S*,8a*R*)-(+)-**10**, and successive dehydrogenation of the adduct obtained gave ketone (3*S*,4*S*,4a*R*,-12b*R*)-(−)-**11**. Air oxidation of (−)-**11** yielded diosphenol, which was converted to triol **12**. To build the furan ring of halenaquinol compounds, the DMSO/DCC/PTFA oxidation reaction of triol **12** was performed. We expected that the oxidation of the primary alcohol of **12** to the aldehyde, subsequent ring closure to form a five-membered ring, and dehydration would give a furan ring, and that the oxidation of the secondary alcohol at the 3-position would yield the final product (**13**). In fact, the reaction of triol **12** proceeded smoothly to give halenaquinol dimethyl ether (12b*S*)-(+)-**13** in 44% overall yield from ketone (−)-**11**.[10]

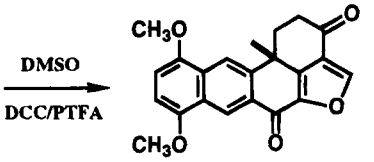
Scheme 1. Synthetic Route to Halenaquinol Dimethyl Ether ((12b*S*)-(+)-13)[10]



9 (4a*S*,7*S*,8*S*,8a*R*)-(+)-**10**



(3*S*,4*S*,4a*R*,12b*R*)-(−)-**11** **12**

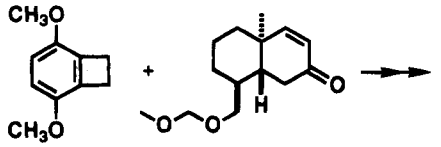


(12b*S*)-(+)-**13**

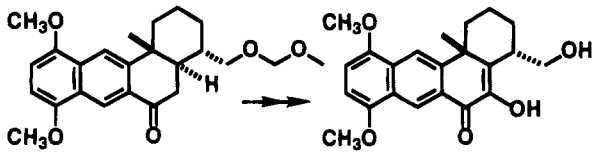
In our previous total synthesis of (+)-xestoquinone (**4**), we applied the same oxidation reaction to diol **16**, which was prepared from (4a*S*,8*S*,8a*S*)-(+)-**14** via (4*S*,4a*R*,-12b*R*)-(−)-**15**.[11] However, it was quite surprising that the desired compound, xestoquinol dimethyl ether (**17**), was never obtained (Scheme 2). Therefore, to make the furan ring, diol **16** was treated with activated manganese(IV) dioxide, and treatment of the resulting crude product with *p*-toluenesulfonic acid (*p*-TsOH) afforded desired xestoquinol dimethyl ether ((12b*S*)-(+)-**17**) in 24% overall yield from ketone **15**.[11] So, it is natural to ask why the DMSO/DCC/PTFA reaction of diol **16** gave no furan product, whereas triol **12** yielded desired furan compound **13**. To answer this question, we reinvestigated the DMSO/DCC/PPTS or PTFA reactions of triol **12** and diol **16** in detail. We found that the DMSO/DCC/PTFA reaction of diol **16** gave dihydrofuran compound **18**, instead of furan **17** (Scheme 3).[14] The dihydrofuran structure was secured by the ^1H NMR and MS spectral data (see the Experimental Section). The formation of **18** implied that the mechanism of the reaction of triol **12** with DMSO/DCC/PPTS or PTFA shown in Scheme 4 might be wrong. We had thought that triol **12** was oxidized to aldehyde **19a**, that subsequent cyclization and dehydration yielded ketofuran alcohol **19c**, and that the secondary alcohol **19c** was oxidized to diketofuran **13**. However, the new reaction mechanism gave insight into the oxidation reaction of triol **12**; dihydrofuran alcohol **8**

(14) When dihydrofuran compound **18** was subjected to the DMSO/DCC/PTFA reaction again, it was recovered unchanged.

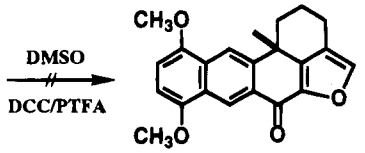
Scheme 2. Synthetic Strategy for Xestoquinol Dimethyl Ether ((12bS)-(+)-17)[11]



9 (4a*S*,8*S*,8a*R*)-(+)-14

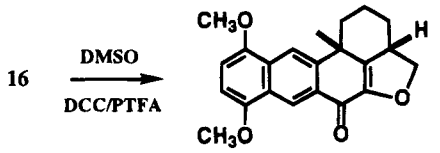


(4*S*,4a*R*,12b*R*)-(−)-15 16



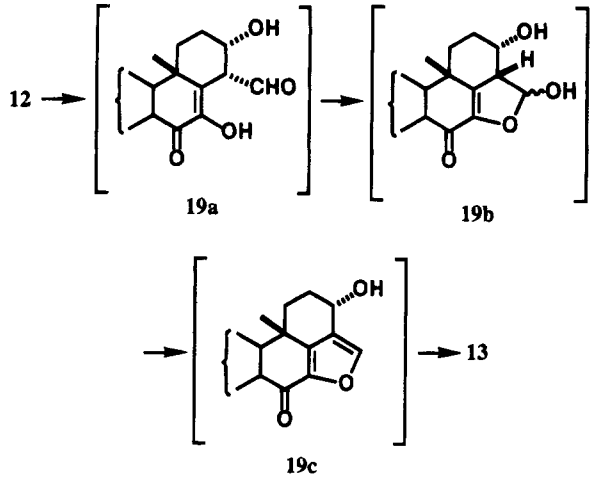
(12b*S*)-(+)-17

Scheme 3



(3a*S*,12b*S*)-18

Scheme 4. Possible Mechanism of Furan Ring Formation

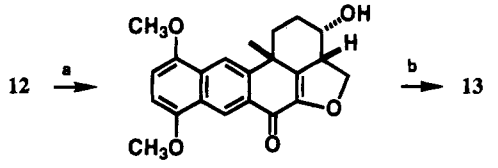


19a 19b 19c

was formed at first, as in the case of diol **16**, and was then oxidized to halenaquinol dimethyl ether (**13**) (Scheme 5).

To confirm the new mechanism, triol **12** was treated with a limited amount of DCC (5.0 equivs) and PPTS (1.3 equivs) in DMSO at room temperature for 2.5 h. Dihydrofuran alcohol intermediate (−)-**8** was obtained in 71% yield as expected. The structure and stereochemistry of **8** were determined from the spectroscopic data, especially the ^{1}H NMR data, which were similar to those of marine natural product **6** isolated earlier by Schmitz from marine

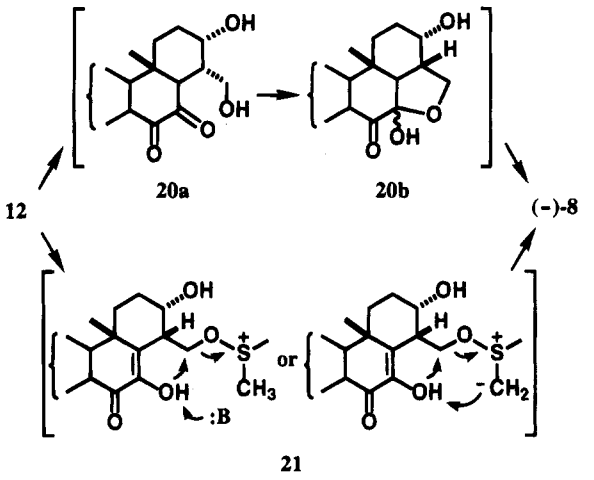
Scheme 5[a]



(3*S*,3a*S*,12b*S*)-(−)-8

[a] (a) DMSO, DCC (5.0 equiv), PPTS (1.3 equiv), benzene, rt, 2.5 h; (b) DMSO, DCC (8.6 equiv), PPTS (6.0 equiv), benzene, rt, 18 h.

Scheme 6. Two Possible Mechanisms of Dihydrofuran Ring Formation



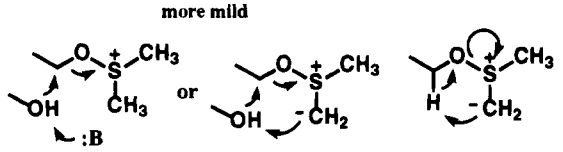
20a 20b 21

sponge *Adocia sp*: **8** δ 1.62 (s, 12b-CH_3), 3.55 (ddd, J = 9.9, 7.2, 3.8 Hz, 3a-H), 4.11 (br s, 3-H), 4.70 (dd, J = 9.9, 9.2 Hz, 4-H), 4.70 (dd, J = 9.2, 7.2 Hz, 4-H); **6** δ 1.63 (s, 12b-CH_3), 3.66 (ddd, J = 10, 6, 4 Hz, 3a-H), 4.36 (br s, 3-H), 4.74 (dd, J = 10, 6 Hz, 4-H), 4.78 (dd, J = 10, 10 Hz, 4-H). It is thus evident that in the DMSO/DCC/PPTS or PTFA reaction, both diol **16** and triol **12** gave dihydrofuran derivatives (**18** and **8**, respectively) as primary products.

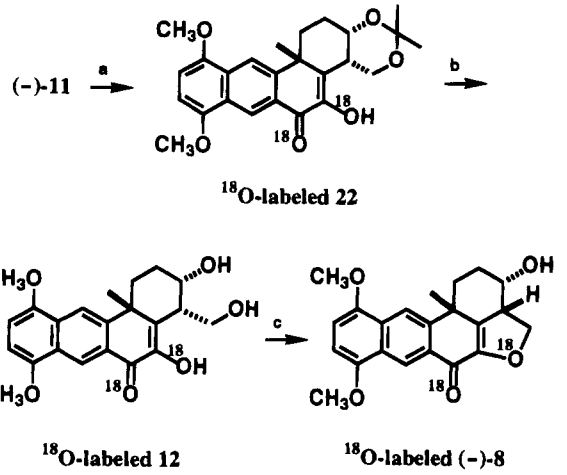
Reaction Mechanism of the Dihydrofuran Ring Formation. As for the mechanism of the dihydrofuran ring formation, there are two possibilities. One is the acid-catalyzed cyclization and dehydration via **20a** and **20b** as shown in Scheme 6. The other possibility is the backside attack of the enol hydroxyl group at the 5-position of sulfonium ylide **21**, formed as an intermediate in the DMSO/DCC/PPTS or PTFA oxidation reaction (Scheme 6). DCC and PPTS or PTFA failed to induce the cyclization reaction in the absence of DMSO. Therefore, the second reaction mechanism is probable. In the usual DMSO/DCC/PPTS or PTFA oxidation reaction,[13] the ylide anion removes the proton of the $HCOS^+$ moiety, and the sulfonium cation withdraws electrons from the S—O bond to yield an aldehyde (Scheme 7). In the case of diol **16** and triol **12**, however, the positively charged sulfur atom of the ylide polarizes the bonding electron-pair of the C—O bond, and the 5-hydroxyl group attacks the carbon atom from the backside to form the dihydrofuran ring because the hydroxyl group is located just behind the carbon (Scheme 7).

It is rather easy to distinguish these two reaction mechanisms; if the cyclization reaction proceeds via the second reaction pathway (intermediate **21** in Scheme 6), when triol **12** ^{18}O-labeled at the enol oxygen is subjected

Scheme 7. Two Pathways of the DMSO/DCC/PPTS or PTFA Reaction



Scheme 8[a]



[a] (a) Potassium *tert*-butoxide, *tert*-butyl alcohol, $^{18}O_2$; (b) 60% aqueous AcOH; (c) DMSO, DCC, PPTS.

to the cyclization reaction, the isotope should be retained throughout the reaction and should be found in the dihydrofuran oxygen. If the reaction proceeds by means of simple acid-catalyzed cyclization (via **20a** and **20b** in Scheme 6), the labeled enol oxygen atom should be eliminated. Oxidation of ketone (−)-**11** under ^{18}O oxygen gas yielded labeled diosphenol **22**, the MS spectrum of which indicated that the product obtained was a mixture of unlabeled, singly labeled, and doubly labeled diosphenols (Scheme 8). The second labeling was assigned to the carbonyl oxygen. To estimate the composition ratio of the mixture, the peak intensity of the MS spectrum of **22** was analyzed; the pattern of peak intensities of the ^{18}O-enriched mixture was well reproduced by a least squares calculation[15] using the pattern of the unlabeled compound (Table 1). From the calculation, the composition of diosphenol **22** was estimated: $^{16}O/^{16}O$, 33.2%; $^{16}O/^{18}O$, 55.3%; $^{18}O/^{18}O$, 11.5%. Although ^{18}O oxygen gas with 97.5% isotope purity was used, the isotope content incorporated in **22** was diminished according to this estimate. One reason for such a decrease is that the solvent and reagents were not degassed. In addition, it seems likely that, since the workup for this labeling reaction used ice-water, the diminished ^{18}O content arises to a significant extent from hydration/dehydration equilibria of the keto/enol system.

Table 1. Observed and Calculated MS Spectral Peak Intensity and Estimated Abundance of Components of ^{18}O-Labeled Diosphenol 22, Triol 12, and Prehalenaquinol Dimethyl Ether ((−)-8)

compound and abundance, %	MS, *m/z*	unlabeled *I* (obsd)	^{18}O-labeled *I* (obsd)	^{18}O-labeled *I* (calcd)
22	422	7.0		
	423			
$^{16}O/^{16}O$: 33.2	424 (M)	100.0	62.8	63.9
$^{16}O/^{18}O$: 55.3	425	28.4	20.1	16.3
$^{18}O/^{18}O$: 11.5	426 (M + 2)	6.4	100.0	100.4
	427		28.8	27.1
	428 (M + 4)		26.0	26.0
12	380	7.8		
	383		9.7	
$^{16}O/^{16}O$: 36.1	384 (M)	100.0	68.3	68.7
$^{16}O/^{18}O$: 52.0	385	25.9	19.0	17.3
$^{18}O/^{18}O$: 11.9	386 (M + 2)	5.8	100.0	100.4
	387		26.6	25.0
	388 (M + 4)		27.3	27.6
	389		6.9	5.7
(−)-**8**	364	13.4	10.2	8.0
	365	4.1		
$^{16}O/^{16}O$: 34.1	366 (M)	100.0	70.6	72.2
$^{16}O/^{18}O$: 54.4	367	25.4	20.1	15.1
$^{18}O/^{18}O$: 11.5	368 (M + 2)	4.2	100.0	100.1
	369		25.4	24.1
	370 (M + 4)		23.9	24.0
	371		5.4	5.1

A mixture of the labeled diosphenols was hydrolyzed to give triol **12**, which was then subjected to the cyclization reaction to give ^{18}O-labeled dihydrofuran **8**. The estimated composition ratio of **8** was almost the same as that of **22**: $^{16}O/^{16}O$, 34.1%; $^{16}O/^{18}O$, 54.4%; $^{18}O/^{18}O$, 11.5% (Table 1). These data clearly indicated that the enol oxygen atom was retained throughout the reaction. Hence the cyclization reaction proceeded by the second reaction mechanism: backside attack of the hydroxyl group in ylide intermediate **21** as shown in Scheme 6. This is a new reaction pathway of the DMSO/ DCC/PPTS or PTFA reagent. It should be noted that this cyclization reaction proceeds under more mild conditions than the DMSO/DCC/PPTS or PTFA oxidation reaction (Scheme 7).

Synthesis of Halenaquinol and Xestoquinol Dimethyl Ethers from the Dihydrofuran Alcohol. When we found that the DMSO/DCC/PTFA reaction of diol **16** gave dihydrofuran **18** instead of the desired furan product, we immediately understood that dihydrofuran alcohol (−)-**8** could be a key synthetic intermediate common to the halenaquinone and xestoquinone natural products. If dihydrofuran alcohol (−)-**8** was dehydrated, the newly formed double bond should migrate to the five-membered ring to give xestoquinol dimethyl ether ((+)-**17**) (Scheme 9). Since the 3α-hydroxyl group and 3aβ-hydrogen of (−)-**8** are *trans*-diaxial, the configuration is ideal for dehydration. On the other hand, if dihydrofuran alcohol (−)-**8** was subjected again to the DMSO/DCC/PPTS reaction, oxidation of the secondary alcohol of **8**

(15) A least squares calculation to estimate the abundance of labeled compounds was performed by use of the following methodology. The following is an example for compound **22**.

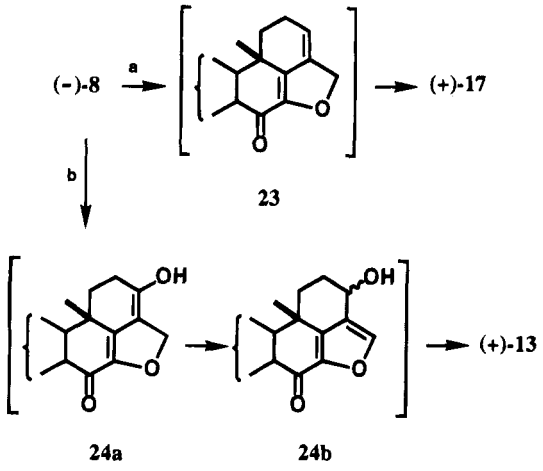
$$x + y + z = 1$$

where x = amount of $^{16}O/^{16}O$ unlabeled compound, y = $^{16}O/^{18}O$ singly labeled compound, and z = $^{18}O/^{18}O$ doubly labeled compound. The observed peak intensity ratio of the unlabeled sample of **22** is the following: (M − 2), 7.0; (M), 100.0; (M + 1), 28.4; (M + 2), 6.4 (Table 1). The observed peak intensity ratio (I_{obs}) of ^{18}O-labeled sample of **22** is the following: (M), 62.8; (M + 1), 20.1; (M + 2), 100.0; (M + 3), 28.8; (M + 4), 26.0. By use of these data, the peak intensity ratio (I_{calc}) of ^{18}O-labeled sample of **22** is calculated as follows: (M), $(100.0x + 7.0y)f$; (M + 1), $(28.4x)f$; (M + 2), $(6.4x + 100.0y + 7.0z)f$; (M + 3), $(28.4x)f$; (M + 4), $(6.4y + 100.0z)f$, where f is a scale factor to normalize the intensity ratio. Next, the R value was minimized by a least squares calculation.

$$R = \sum\{(I_{calc} - I_{obs})/I_{obs}\}^2$$

A computer program was prepared, and the average R value for **22** was calculated to be 5.4%.

Scheme 9[a]



[a] (a) *p*-TsOH; (b) DMSO, DCC, PPTS.

should yield enol **24a** or furan alcohol intermediate **24b**, which would be further oxidized to give halenaquinol dimethyl ether (+)-**13**. These expectations were confirmed.

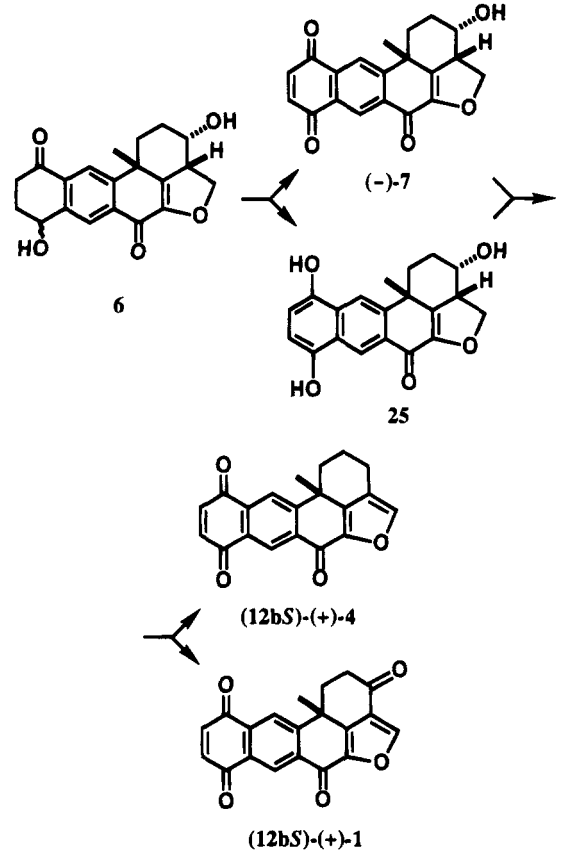
A solution of dihydrofuran alcohol (−)-**8** in benzene was refluxed for 24 h in the presence of *p*-TsOH to yield xestoquinol dimethyl ether ((+)-**17**) in 77% yield as expected. Compound (+)-**17** had previously been converted to xestoquinone (+)-**4** and xestoquinol.[11] This synthetic route is more efficient and more elegant than our previous total synthesis of xestoquinone and xestoquinol. Treatment of dihydrofuran alcohol (−)-**8** with DCC (8.6 equiv) and PPTS (6.0 equiv) in DMSO at room temperature for 24 h gave halenaquinol dimethyl ether ((+)-**13**) in 85% yield. Halenaquinone ((+)-**1**) and halenaquinol ((+)-**2**) had previously been synthesized from compound (+)-**13**.[10] We have thus achieved the formal total synthesis of xestoquinol and halenaquinol compounds from the common synthetic intermediate (−)-**8**.

Synthesis and Absolute Stereochemistry of Prehalenaquinone and Prehalenaquinol, Putative Biosynthetic Precursors Common to Halenaquinone and Xestoquinone Compounds. The chemical conversion of dihydrofuran alcohol (−)-**8** to xestoquinol and halenaquinol compounds discussed above is a very attractive possible route for the biosynthesis of these natural products in living marine sponges; that is, dihydrofuran alcohol quinone **7** and dihydrofuran alcohol hydroquinone **25** are possible biosynthetic precursors (Scheme 10). As in the case of the chemical conversion, dehydration of **7** or **25** would lead to xestoquinone (**4**) or xestoquinol, and oxidation of **7** or **25** would lead to halenaquinone (**1**) or halenaquinol (**2**). The related compound, dihydrofuran alcohol **6**, isolated by Schmitz[5] may be an earlier intermediate than precursors **7** and **25**, as shown in Scheme 10. Oxidation of the secondary alcohol group in the A ring of **6** would give a diketone, which would be expected to isomerize to hydroquinone compound **25**. Hydroquinone **25** should be easily oxidized to quinone **7**. Therefore, we thought that if the biosynthesis of halenaquinone and xestoquinone compounds proceed as postulated here, biosynthetic precursors **7** and/or **25** should be contained in marine sponges.

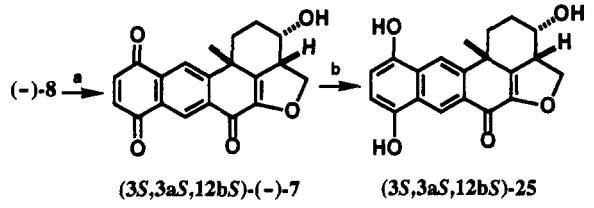
Authentic samples of putative biosynthetic precursors (−)-**7** and **25** were synthesized (Scheme 11). Treatment of dimethyl ether (−)-**8** with ammonium cerium(IV) nitrate (CAN) afforded quinone (−)-**7** in 79% yield, which was then quantitatively converted to hydroquinone **25** by treatment with sodium hydrosulfite. The structure of these compounds was confirmed by the spectroscopic and physical data shown in the Experimental Section. Since the ^{1}H NMR spectrum of **7** in $CDCl_3$ showed a complex pattern in the aromatic region, a trace of trifluoroacetic acid was added to the $CDCl_3$ solution, and a simpler spectral pattern that was assignable to structure **7** was obtained.[16] It should be noted that Schmitz also used a mixed solvent of $CDCl_3$/trifluoroacetic acid to measure the ^{1}H NMR spectrum of natural dihydrofuran compound **6**. Since these synthetic dihydrofuran alcohols were derived from (3*S*,4*S*,4a*R*,12b*R*)-(−)-**11**, it is certain that the absolute stereochemistry of (−)-**7** and **25** is (3*S*,3a*S*,12b*S*). The putative biosynthetic precursors, (−)-**7** and **25**, were named prehalenaquinone and prehalenaquinol, respectively.

Isolation of Prehalenaquinone from an Okinawan Marine Sponge, *Xestospongia sapra*. We

Scheme 10. Putative Biosynthetic Route to Halenaquinone and Xestoquinone Compounds



Scheme 11[a]



[a] (a) CAN, water, CH_3CN; (b) $Na_2S_2O_4$, water, acetone.

(16) The reason for the complex NMR of **7** has not been clarified yet, although hydration or hydrogen bonding is probable.

next tried to determine whether putative biosynthetic precursors prehalenaquinone ((−)-**7**) and prehalenaquinol (**25**) were actually contained in marine sponges. Using (−)-**7** and **25** as authentic samples, we analyzed by HPLC the component of the extract of an Okinawan marine sponge *Xestospongia sapra* from which halenaquinone ((+)-**1**) and xestoquinone ((+)-**4**) had been isolated.[3,4]

The fresh acetone extract of the sponge was analyzed by HPLC (Inertsil silica gel; EtOAc/hexane/MeOH 100:100:5) and also by reverse phase HPLC (ODS C_{18} column; 50% aqueous MeOH). Although no peak corresponding to prehalenaquinol (**25**) was detected, a peak corresponding to prehalenaquinone ((−)-**7**) was found in both chromatograms. Therefore, we performed the isolation of prehalenaquinone (**7**). The wet sponge (305 g) was treated with acetone, and the aqueous acetone solution obtained was extracted with ethyl acetate to give a crude extract (6.5 g), which was successively separated and purified by HPLC (see the Experimental Section) to give prehalenaquinone (**7**) (8.3 mg). The spectral and physical data, including the CD data, of natural **7** thus isolated were identical with those of synthetic (−)-**7** (see the Experimental Section). These results imply that dihydrofuran alcohol **7** may be a biosynthetic precursor of halenaquinone and xestoquinone compounds.

Concluding Remarks

The total synthesis of (3*S*,3a*S*,12b*S*)-(−)-prehalenaquinone (**7**), a putative biosynthetic precursor common to halenaquinone and xestoquinone compounds isolated from tropical marine sponges, was achieved, although the compound had not been isolated from a sponge at the time of the synthesis. One of the criticisms of our first total synthesis of halenaquinone compounds, as summarized in Scheme 1, was that the chiralities at the 3- and 4-positions in (−)-**11** were lost in the final product (+)-**2**. These chiralities, however, were all directly used in (3*S*,3a*S*,12b*S*)-(−)-prehalenaquinone (**7**) and also in synthetic intermediate (−)-**8**.

On the basis of our synthetic studies of halenaquinone and xestoquinone compounds, it occurred to us that these synthetic routes might simulate the actual biosynthesis, and we predicted the existence of dihydrofuran alcohol compounds (−)-**7** and/or **25** as the natural biosynthetic intermediates. After our total synthesis of (−)-**7**, we actually succeeded in isolating (3*S*,3a*S*,12b*S*)-(−)-prehalenaquinone (**7**) from a marine sponge. These results imply that halenaquinone (**1**) and xestoquinone (**4**), cardiotonic marine natural products with a novel molecular skeleton, may be biosynthesized via the dihydrofuran alcohol precursor.

The new cyclization reaction to form dihydrofuran compounds with DMSO/DCC/PPTS or PTFA was discovered, and the reaction proceeds under more mild conditions than the commonly used DMSO/DCC/PPTS or PTFA oxidation pathway. We are exploring the application of this new reaction pathway to the synthesis of dihydrofuran compounds.

Experimental Section

General Procedures. Melting points are uncorrected. IR spectra were obtained as KBr disks on a JEOL JIR-100 or a Hitachi 285 spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL FX90Q (89.6 MHz), a Bruker AC-250 (250.1 MHz), or a JEOL GSX-500 (500.0 MHz) spectrometer. ^{13}C NMR spectra were obtained on a Bruker AC-250 (62.9 MHz) or a JEOL GSX-500 (125.7 MHz) spectrometer. All NMR data are reported in ppm (δ) downfield from TMS. Optical rotations $[\alpha]_D$ were measured on a Jasco DIP-370 spectropolarimeter. UV and CD spectra were recorded on Jasco Ubest-50 and Jasco J-400X spectrometers, respectively. MS spectra were obtained with a JEOL JMS DX-300/JMA-3100/3500 spectrometer by the electron ionization procedure (70 eV), unless otherwise noted. The purities of the title compounds were shown to be ≥95% by ^{1}H NMR, TLC, HPLC, and/or elemental analysis.

(3a*S*,12b*S*)-2,3,3a,4-Tetrahydro-8,11-dimethoxy-12b-methyl-1*H*-benzo[6,7]phenanthro[10,1-*bc*]furan-6(12b*H*)-one (18). To a solution of (4*S*,12b*S*)-1,2,3,4-tetrahydro-5-hydroxy-4-(hydroxymethyl)-8,11-dimethoxy-12b-methyl-6(12b*H*)-benz[*a*]anthracenone (**16**)[11] (0.031 g, 0.084 mmol) in benzene (6 mL) was added a solution of pyridine (0.049 g, 0.62 mmol) and TFA (0.037 g, 0.32 mmol) in DMSO (2 mL), and then DCC (0.155 g, 0.753 mmol) was added. The reaction mixture was stirred at rt for 20 h, poured into ice-water, and extracted with ethyl acetate. The organic layer was washed with brine and evaporated to dryness, to give an oil. Chromatography of the crude product on silica gel (hexane/EtOAc 1:1) yielded dihydrofuran derivative **18** (0.015 g, 51%) as a yellow syrup: ^{1}H NMR (89.55 MHz, $CDCl_3$) δ 1.60 (3 H, s), 1.0−2.3 (5 H, m), 2.50 (1 H, br d, J = 11.8 Hz), 3.2−3.6 (1 H, m), 3.96 (3 H, s), 3.97 (3 H, s), 4.20 (1 H, dd, J = 9.3, 6.1 Hz), 4.74 (1 H, dd, J = 9.8, 9.3 Hz), 6.68 (1 H, d, J = 8.4 Hz), 6.76 (1 H, d, J = 8.4 Hz), 8.31 (1 H, s), 9.21 (1 H, s); MS m/z 350 (M^+, relative intensity 80%), 335 (100), 307 (19), 228 (21), 87 (11).

Prehalenaquinol Dimethyl Ether, (3*S*,3a*S*,12b*S*)-(−)-2,3,3a,4-Tetrahydro-3-hydroxy-8,11-dimethoxy-12b-methyl-1*H*-benzo[6,7]phenanthro[10,1−*bc*]furan-6(12b*H*)-one (8). To a solution of (3*S*,4*S*,12b*S*)-1,2,3,4-tetrahydro-3,5-dihydroxy-4-(hydroxymethyl)-8,11-dimethoxy-12b-methyl-6(12b*H*)benz[*a*]anthracenone (**12**)[10] (0.094 g, 0.245 mmol) in benzene (15 mL) were added DCC (0.253 g, 1.226 mmol), DMSO (1 mL), and PPTS (0.080 g, 0.318 mmol). The reaction mixture was stirred at rt for 2.5 h, poured into ice-water, and extracted with ethyl acetate. The organic layer was washed with brine and evaporated in vacuo. HPLC of the residue on silica gel (EtOAc) yielded prehalenaquinol dimethyl ether **8** (0.064 g, 71%) as yellow crystals: mp 269 °C dec; TLC (silica gel, hexane/ EtOAc 1:1) R_f 0.16; IR (KBr) ν_{max} 3406, 2926, 1655, 1623, 1465, 1267, 1244, 1165, 1111, 1090, 1065, 966, 806, 721 cm^{-1}; ^{1}H NMR (500.0 MHz, $CDCl_3$) δ 1.62 (3 H, s), 1.87 (1 H, ddd, J = 13.9, 13.5, 4.0 Hz), 1.99 (1 H, dddd, J = 14.1, 4.0, 3.4, 3.4 Hz), 2.06 (1 H, dddd, J = 14.1, 13.9, 3.4, 2.7 Hz), 2.34 (1 H, ddd, J = 13.5, 3.4, 2.7 Hz), 3.55 (1 H, ddd, J = 9.9, 7.2, 3.8 Hz), 3.96 (3 H, s), 3.98 (3 H, s), 4.11 (1 H, br s, $W_{1/2}$ = 13.0 Hz), 4.70 (1 H, dd, J = 9.9, 9.2 Hz), 4.70 (1 H, dd, J = 9.2, 7.2 Hz), 6.67 (1 H, d, J = 8.4 Hz), 6.79 (1 H, d, J = 8.4 Hz), 8.32 (1 H, s), 9.20 (1 H, s); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 25.61, 29.02, 34.73, 38.18, 47.20, 55.61, 55.72, 67.89, 71.29, 103.06, 105.67, 119.02, 122.94, 124.82, 127.72, 129.88, 137.31, 146.70, 148.05, 148.66, 150.78, 176.29; $[\alpha]_D$ −6.0° (c 0.914, $CHCl_3$); UV (EtOH) λ_{max} 397.4 nm (ϵ 4 200), 330.4 (7 400), 279.2 (17 600), 223.4 (34 700); CD (EtOH) λ_{ext} 397.0 nm ($\Delta\epsilon$ +0.7), 357.5 (0.0), 326.0 (−3.8), 293.0 (0.0), 281.0 (+2.0), 235.0 (+3.4); MS m/z 366 (parent, relative intensity 100%), 351 (75), 348 (43), 333 (58), 309 (61), 307 (42); high-resolution mass spectrum (HRMS), calcd for $C_{22}H_{22}O_5$ 366.14671, found 366.14680. Anal. Calcd for $C_{22}H_{22}O_5$: C, 72.12; H, 6.05. Found: C, 71.67; H, 6.27.

^{18}O-Labeled (3*S*,4*S*,12b*S*)-1,2,3,4-Tetrahydro-3,5-dihydroxy-4-(hydroxymethyl)-8,11-dimethoxy-12b-methyl-6(12b*H*)-benz[*a*]anthracenone Acetonide (22). In a flask was placed (3*S*,4*S*,4a*R*,12b*R*)-(−)-1,2,3,4,4a,12b-hexahydro-3-hydroxy-4-(hydroxymethyl)-8,11-dimethoxy-12b-methyl-6(5*H*)-benz[*a*]anthracenone acetonide (**11**)[10] (0.058 g, 0.141 mmol). After the flask was degassed, it was charged with $^{18}O_2$ gas (isotope purity, 97.5%; 100 mL), and then a solution of potassium *tert*-butoxide (0.159 g, 1.41 mmol) in *tert*-butyl alcohol (15 mL) was added. The reaction mixture was vigorously stirred at rt for 2 h, poured into ice-water, and extracted with ethyl acetate. The organic layer was washed with brine and evaporated in vacuo. The residue obtained was washed with petroleum ether to give ^{18}O-labeled diosphenol **22** (0.037

g, 62%) as a yellow powder: MS m/z 428 (relative intensity 13%), 427 (14), 426 (parent, 50), 425 (10), 424 (30), 370 (25), 369 (26), 368 (100), 367 (22), 366 (71); HRMS, calcd for $C_{25}H_{28}O_5{}^{18}O$ 426.19283, found 426.19262. Other spectral data were identical with those of the unlabeled authentic sample.[10]

^{18}O-Labeled (3*S*,4*S*,12b*S*)-1,2,3,4-Tetrahydro-3,5-dihydroxy-4-(hydroxymethyl)-8,11-dimethoxy-12b-methyl-6(12b*H*)-benz[*a*]anthracenone (12). A mixture of ^{18}O-labeled acetonide (3*S*,4*S*,12b*S*)-**22** (0.037 g, 0.087 mmol) and 60% acetic acid (10 mL) was stirred at rt for 30 min. The reaction mixture was poured into water and extracted with chloroform. The organic layer was washed with brine and evaporated in vacuo to yield ^{18}O-labeled triol **12** (0.034 g, 100%): MS m/z 388 (relative intensity 6%), 387 (6), 386 (parent, 23), 385 (5), 384 (16), 368 (66), 366 (90), 311 (75), 309 (100). Other spectral data were identical with those of the unlabeled authentic sample.[10]

^{18}O-Labeled Prehalenaquinol Dimethyl Ether, (3*S*,3a*S*,12b*S*)-2,3,3a,4-Tetrahydro-3-hydroxy-8,11-dimethoxy-12b-methyl-1*H*-benzo[6,7]phenanthro[10,1-*bc*]furan-6(12b*H*)-one (8). To a solution of ^{18}O-labeled triol (3*S*,4*S*,12b*S*)-**12** (0.034 g, 0.088 mmol) in benzene (10 mL) were added DCC (0.105 g, 0.508 mmol), DMSO (1 mL), and PPTS (0.031 g, 0.122 mmol). The reaction mixture was stirred at rt for 2.5 h, poured into ice-water, and extracted with ethyl acetate. The organic layer was washed with brine and evaporated in vacuo. HPLC of the residue on silica gel (EtOAc) yielded ^{18}O-labeled dihydrofuran alcohol **8** (0.028 g, 75%): MS m/z 370 (relative intensity 24%), 369 (25), 368 (parent, 100), 367 (20), 366 (71), 353 (56), 335(70), 311 (70), 309 (82); HRMS, calcd for $C_{22}H_{22}O_4{}^{18}O$ 368.15097, found 368.15084. Other spectral data were identical with those of the unlabeled authentic sample (−)-**8**.

DMSO/DCC/PPTS Oxidation of Prehalenaquinol Dimethyl Ether (3*S*, 3a*S*,12b*S*)-(−)-8. To a solution of dihydrofuran alcohol **8** (0.025 g, 0.068 mmol) in benzene (5 mL) and DMSO (5 mL) were added DCC (0.120 g, 0.582 mmol) and PPTS (0.104 g, 0.410 mmol). The reaction mixture was stirred at rt overnight, poured into ice-water, and extracted with ethyl acetate. The organic layer was washed with brine and evaporated in vacuo. HPLC of the residue on silica gel (hexane/EtOAc 2:3) yielded halenaquinol dimethyl ether (12b*S*)-(+)-**13** (0.021 g, 85%) as crystals. Its spectral data were identical with those of the authentic sample **13**.[10]

Dehydration of Prehalenaquinol Dimethyl Ether (3*S*,3a*S*,12b*S*)-(−)-8. A mixture of dihydrofuran alcohol **8** (0.015 g, 0.041 mmol), benzene (7 mL), and *p*-TsOH (0.005 g, 0.029 mmol) was stirred under reflux overnight. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with brine and evaporated in vacuo. HPLC of the residue on silica gel (hexane/EtOAc 1:1) yielded xestoquinol dimethyl ether ((12b*S*)-(+)-**17**) (0.011 g, 77%) as yellow crystals. Its spectral data were identical with those of the authentic sample **17**.[11]

Synthesis of Prehalenaquinone, (3*S*,3a*S*,12b*S*)-(−)-2,3,3a,4-Tetrahydro-3-hydroxy-12b-methyl-1*H*-benzo[6,7]phenanthro[10,1-*bc*]furan-6,8,11(12b*H*)-trione (7). To a stirred solution of (3*S*,3a*S*,12b*S*)-(−)-prehalenaquinol dimethyl ether (**8**) (0.040 g, 0.109 mmol) in acetonitrile (20 mL) cooled in an ice−salt bath was added dropwise over 3 min a solution of CAN (0.144 g, 0.262 mmol) in water (1.2 mL). After 5 min, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine and evaporated in vacuo. HPLC of the residue on silica gel (EtOAc) yielded (3*S*,3a*S*,12b*S*)-(−)-prehalenaquinone **7** (0.029 g, 79%) as crystals: mp 207 °C; TLC (silica gel, EtOAc) R_f 0.53; IR (KBr) ν_{max} 3452, 2945, 1670, 1603, 1335, 1296, 1138, 1057, 1026, 849, 434 cm^{-1}; ^{1}H NMR (250.1 MHz, $CDCl_3$) δ 1.60 (3 H, s), 1.88 (1 H, ddd, J = 12.6, 12.6, 5.5 Hz), 1.97−2.10 (2 H, m), 2.28 (1 H, ddd, J = 12.6, 3.0, 3.0 Hz), 3.54 (1 H, ddd, J = 9.2, 7.7, 3.9 Hz), 4.16 (1 H, ddd, J = 3.9, 2.8, 2.8 Hz), 4.71 (1 H, dd, J = 9.4, 9.2 Hz), 4.72 (1 H, dd, J = 9.4, 7.7 Hz), 7.04 (2 H, s), 8.26 (1 H, s), 8.89 (1 H, s); ^{1}H NMR (250.1 MHz, $CDCl_3$/trace of trifluoroacetic acid) δ 1.61 (3 H, s), 1.86 (1 H, ddd, J = 12.5, 12.5, 5.2 Hz), 1.95−2.10 (2 H, m), 2.28 (1 H, ddd, J = 12.7, 3.1, 3.1 Hz), 3.54 (1 H, ddd, J = 8.5, 8.5, 3.9 Hz), 4.16 (1 H, ddd, J = 3.9, 2.9, 2.9 Hz), 4.72 (2 H, d, J = 8.5 Hz), 7.05 (2 H, s), 8.27 (1 H, s), 8.95 (1 H, s); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 24.39, 28.67, 29.70, 33.66, 39.25, 47.18, 67.56, 71.56, 124.52, 126.31, 130.31, 133.27, 136.26, 138.81, 139.47, 148.09, 156.11, 174.06, 183.73, 184.64; $[\alpha]_D$ −47.5° (c 0.747, $CHCl_3$); UV (MeOH) λ_{max} 360.0 nm (ϵ 4 600), 314.4 (7 700), 262.0 (sh, 21 300), 253.6 (21 700), 215.6 (24 900); CD (MeOH) λ_{ext} 335.0 nm ($\Delta\epsilon$ −1.8), 285.0 (0.0), 250.0 (+3.9); MS m/z 336 (parent, relative intensity 48%), 303 (27), 279 (88), 277 (100); HRMS, calcd for $C_{20}H_{16}O_5$ 336.09977, found 336.09985. Anal. Calcd for $C_{20}H_{16}O_5$: C, 71.42; H, 4.79. Found: C, 71.68; H, 5.06.

Synthesis of Prehalenaquinol, (3*S*,3a*S*,12b*S*)-2,3,3a,4-Tetrahydro-3,8,11-trihydroxy-12b-methyl-1*H*-benzo[6,7]-phenanthro[10,1-*bc*]furan-6(12b*H*)-one (25). To a solution of (3*S*,3a*S*,12b*S*)-(−)-quinone **7** (0.015 g, 0.045 mmol) in acetone (15 mL) was added an aqueous solution of $Na_2S_2O_4$ (10%, 1 mL), and then the reaction mixture was stirred at rt for 45 min. After addition of dichloromethane (20 mL) and anhyd sodium sulfate, the organic layer was separated and evaporated in vacuo. The residue obtained was dissolved in a mixture of acetone and dichloromethane, and the solution was dried over anhyd Na_2SO_4. The organic layer was evaporated in vacuo, and the residue was washed with dichloromethane and diethyl ether to give prehalenaquinol **25** (0.015 g, 100%) as a powder: TLC (silica gel, EtOAc) R_f 0.43; IR (KBr) ν_{max} 3305, 2972, 2935, 1651, 1626, 1396, 1296, 1246, 1149, 1103, 1043, 823, 762, 737 cm^{-1}; ^{1}H NMR (89.6 MHz, DMSO-d_6) δ 1.54 (3 H, s), 1.60−2.30 (4 H, m), 3.53 (1 H, m), 3.92 (1 H, br s), 4.52 (2 H, d, J = 8.6 Hz), 4.75 (1 H, br s, disappeared in D_2O/DMSO-d_6), 6.65 (1 H, d, J = 8.8 Hz), 6.80 (1 H, d, J = 8.8 Hz), 8.23 (1 H, s), 8.85 (1 H, s), 9.46 (1 H, s, disappeared in D_2O/DMSO-d_6), 9.63 (1 H, s, disappeared in D_2O/DMSO-d_6); UV (MeOH) λ_{max} 416.0 nm (ϵ 3200), 328.0 (7400), 280.0 (16 200), 224.4 (29 100); CD (MeOH) λ_{ext} 420.0 nm ($\Delta\epsilon$ +0.5), 325.0 (−4.5), 293.5 (0.0), 282.0 (+2.1); MS m/z 338 (parent, relative intensity 16%), 336 (15), 320 (23), 305 (55), 303 (100); HRMS, calcd for $C_{20}H_{18}O_5$ 338.11542, found 338.11560.

Isolation of (3*S*,3a*S*,12b*S*)-(−)-Prehalenaquinone (7) from a Marine Sponge *Xestospongia sapra*. To the frozen wet sample (305 g) of an Okinawan marine sponge, *X. sapra*, was added acetone (1000 mL), and the mixture was allowed to stand at rt for 1 h, during which time the mixture was occasionally ultrasonicated. The mixture was filtered through Celite, and the insoluble material was washed with acetone (700 mL). The filtrates were combined (1700 mL) and evaporated, in vacuo, below 38 °C. To the residue obtained was added water (400 mL), and the mixture was extracted with ethyl acetate (total volume 1000 mL). The organic layer was washed with water, dried over anhyd Na_2SO_4, and evaporated, in vacuo, below 45 °C, to give a crude extract (6.5 g). The crude extract was successively separated and purified by column chromatography (silica gel, EtOAc), preparative HPLC (silica gel, hexane/EtOAc 1:3), and another preparative HPLC (silica gel, hexane/EtOAc/MeOH 100:100:2) to give prehalenaquinone (**7**) (0.0083 g, 0.13% from the crude extract (6.5 g)): IR (KBr) ν_{max} 3444, 2943, 1670, 1603, 1333, 1296, 1138, 1055, 1026, 847, 434 cm^{-1}; ^{1}H NMR (250.1 MHz, $CDCl_3$/trace of trifluoroacetic acid) δ 1.60 (3 H, s), 1.86 (1 H, ddd, J = 12.6, 12.5, 5.1 Hz), 1.95−2.10 (2 H, m), 2.28 (1 H, ddd, J = 12.6, 3.1, 3.1 Hz), 3.54 (1 H, ddd, J = 8.5, 8.5, 3.9 Hz), 4.16 (1 H, ddd, J = 3.9, 3.1, 3.1 Hz), 4.71 (2 H, d, J = 8.5 Hz), 7.05 (2 H, s), 8.26 (1 H, s), 8.95 (1 H, s); UV (MeOH) λ_{max} 360.0 nm (ϵ 4300), 314.0 (7900), 262.0 (sh, 20 300), 253.6 (20 800), 215.8 (24 300); CD (MeOH) λ_{ext} 335.0 nm ($\Delta\epsilon$ −1.6), 284.0 (0.0), 250.0 (+3.8); MS m/z 336 (parent, relative intensity 59%), 280 (37), 279 (100), 277 (16). These spectral data are identical with those of synthetic (3*S*,3a*S*,12b*S*)-(−)-prehalenaquinone.

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Supplementary Material Available: The full listing of ^{1}H NMR data, complete with peak assignments (1 page). 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.