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Absolute Stereochemistry of the Halenaquinol Family, Marine Natural Products with a Novel Pentacyclic Skeleton, As Determined by the Theoretical Calculation of Circular Dichroism Spectra

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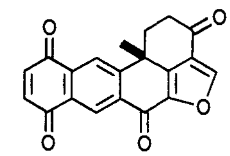
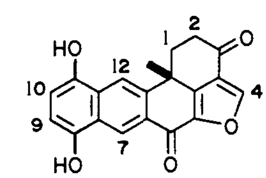
Contribution from the Chemical Research Institute of Nonaqueous Solutions, Tohoku University, 2-1-1 Katahira, Sendai 980, Japan, and the Faculty of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565, Japan. *Received December 9, 1988*

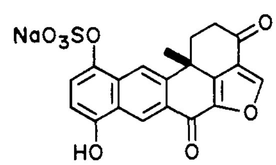
Abstract: The absolute stereostructures of halenaquinone (+)-**1**, halenaquinol (+)-**2**, and halenaquinol sulfate (+)-**3**, novel pentacyclic marine natural products isolated from tropical sea sponges *Xestospongia exigua* and *sapra*, were determined by the theoretical calculation of CD spectra. Halenaquinol dimethyl ether (+)-**7** was converted to naphthalene-diene derivatives **12**–**15**, which exhibited strong CD Cotton effects due to the twisted π-electron system composed of the naphthalene-diene moiety: for example, (−)-**12** showed three major Cotton effects, λ_{ext} 338 nm ($\Delta\epsilon$ +6.4), 301 nm ($\Delta\epsilon$ −23.3), and 229 nm ($\Delta\epsilon$ +40.9) in the region of the $\pi \rightarrow \pi^*$ UV absorption bands, λ_{max} 324 nm (ϵ 27 000) and λ_{max} 218 nm (ϵ 42 000). Therefore, these derivatives with a twisted π-electron chromophore are ideal systems for the determination of the absolute stereochemistry by the application of the π-electron SCF-CI-dipole velocity MO method. As a model compound for the theoretical calculation of CD spectra, we adopted the molecule **16**, the absolute configuration of which was arbitrarily chosen to be 12b*S*. The calculated CD and UV values of the model compound **16** were in a good agreement with the observed data of **12** and other naphthalene-diene derivatives: the calculated CD data of **16**, λ_{ext} 378 nm ($\Delta\epsilon$ +3.3), λ_{ext} 322 nm ($\Delta\epsilon$ −22.4), and λ_{ext} 223 nm ($\Delta\epsilon$ +35.5); the calculated UV data of **16**, λ_{max} 349 nm (ϵ 29 900) and λ_{max} 219 nm (ϵ 40 300). Accordingly, the absolute stereochemistry of halenaquinol (+)-**2** was theoretically determined to be 12b*S*. Since halenaquinone and halenaquinol sulfate had been already chemically correlated to halenaquinol, the absolute stereostructures of halenaquinone (+)-**1** and halenaquinol sulfate (+)-**3** were also established to be 12b*S*, respectively. The cardiotonic activity of halenaquinol was also studied.

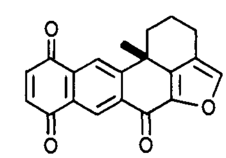
In recent years, there has been considerable interest in the chemistry and biological activity of novel marine natural products isolated from marine sponges. For example, Scheuer and coworkers isolated halenaquinone (**1**-, Chart I), an antibiotic with a novel pentacyclic skeleton, from a tropical marine sponge of *Xestospongia exigua* collected in Western Caroline Islands, and determined its relative structure by the X-ray crystallographic method.[2] One group of the authors also isolated halenaquinol (**2**), a hydroquinone form of halenaquinone, from the Okinawan marine sponge *Xestospongia sapra*, together with halenaquinol sulfate (**3**).[3] Furthermore, Nakamura and co-workers isolated xestoquinone (**4**) from the same Okinawan sponge as a powerful cardiotonic constituent.[4] More recently, Schmitz and his coworker isolated 3-ketoadociaquinone A (**5**), a partially reduced derivative (**6**) of halenaquinone, and related compounds from a marine sponge, *Adocia sp.* from Truk Lagoon, in addition to halenaquinone and xestoquinone.[5] They also revealed that some of these novel marine natural products also showed cytotoxicity.[5] For such an increasing interest on the physiological activity of the novel compounds of the halenaquinol family, it is quite significant to determine the absolute stereochemistry of these compounds. Here we report the absolute stereostructures of halenaquinone (**1**), halenaquinol (**2**), and halenaquinol sulfate (**3**) as determined by the theoretical calculation of the CD spectra of pertinent derivatives.[6,7]

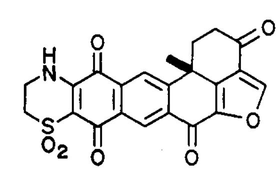
Chart I

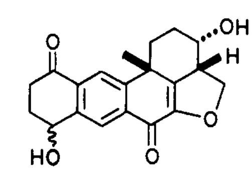

(12bS)-(+)-1


(12bS)-(+)-2


(12bS)-(+)-3


(+)-4


(+)-5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Recently, the theoretical calculation of the CD spectra by the π-electron SCF-CI-dipole velocity MO method[8-12] has become an important tool in the absolute configurational study of a variety

(1) (a) Tohoku University. (b) Osaka University.
(2) Roll, D. M.; Scheuer, P. J.; Matsumoto, G. K.; Clardy, J. *J. Am. Chem. Soc.* **1983**, *105*, 6177.
(3) Kobayashi, M.; Shimizu, N.; Kyogoku, Y.; Kitagawa, I. *Chem. Pharm. Bull.* **1985**, *33*, 1305.
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(5) Schmitz, F. J.; Bloor, S. J. *J. Org. Chem.* **1988**, *53*, 3922.
(6) A preliminary report of this work: Kobayashi, M.; Shimizu, N.; Kitagawa, I.; Kyogoku, Y.; Harada, N.; Uda, H. *Tetrahedron Lett.* **1985**, *26*, 3833.
(7) For the total synthesis and experimental determination of the absolute stereostructures of (+)-halenaquinol and (+)-halenaquinone, see: Harada, N.; Sugioka, T.; Ando, Y.; Uda, H.; Kuriki, T. *J. Am. Chem. Soc.* **1988**, *110*, 8483.
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(9) Kemp, C.; Mason, S. F. *Tetrahedron* **1966**, *22*, 629. Brown, A.; Kemp, C.; Mason, S. F. *J. Chem. Soc. A* **1971**, 751.
(10) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy—Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983.
(11) Rosini, C.; Bertucci, C.; Salvadori, P.; Zandomeneghi, M. *J. Am. Chem. Soc.* **1985**, *107*, 17.
(12) See also: Roschster, J.; Berg, U.; Pierrot, M.; Sandstrom, J. *J. Am. Chem. Soc.* **1987**, *109*, 492.

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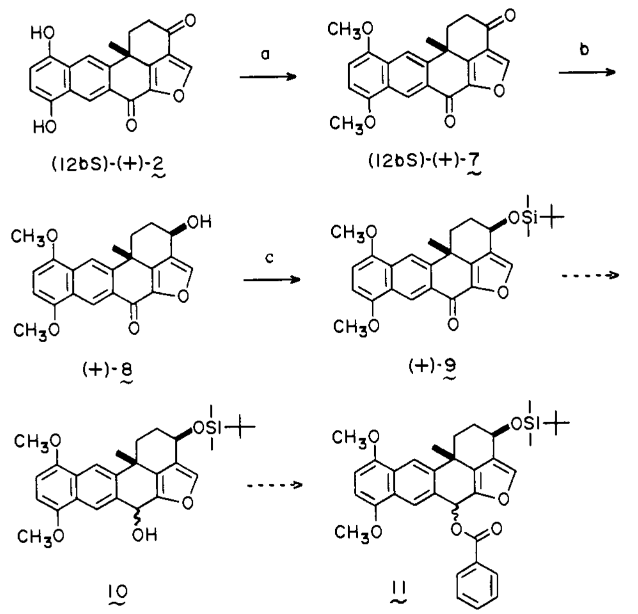
Scheme I[a]



[a] (a) CH_3I, K_2CO_3, acetone; (b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, CH_2Cl_2; (c) *tert*-Butylchlorodimethylsilane, imidazole, *N*,*N*-dimethylformamide (DMF).

of twisted and conjugated π-electron systems. In fact, we have recently determined the absolute stereochemistry of (+)-1,8a-dihydro-3,8-dimethylazulene, a labile biosynthetic intermediate for 1,4-dimethylazulene isolated from a liverwort, by the application of the present method to the theoretical calculation of the CD spectra of the twisted tetraene system.[13] In that case, we have also succeeded in the experimental verification of the absolute configuration theoretically determined, by the comparison of the CD spectra of the natural product with those of synthetic chiral model compounds.[13] Moreover, we have theoretically determined the absolute stereochemistry of novel chiral troponoid spiro compounds in a similar way;[14] the conclusion of the absolute configuration theoretically obtained was consistent with that of X-ray crystallographic studies. The π-electron SCF-CI-DV MO method is thus powerful for nonempirical determination of the absolute configuration of twisted and conjugated π-electron systems. In this paper, we report the application of the present method to the more complicated system of the natural products of the halenaquinol family and also clarify the scope and limitation of this CD method.[6,7]

Methods of Calculation

Molecular Geometry. The stereochemical geometry of halenaquinol trans-methoxy diene derivative (3*R*,4*R*,12b*S*)-(−)-**14** and the model compound (12b*S*)-**16** was calculated by the molecular mechanics (MMP2)[15] to give the stable conformations depicted in Figure 3. The molecular framework of these compounds is relatively rigid, and the D ring takes a half-chair conformation.

Numerical Calculation of CD and UV Spectra. The CD and UV spectra of the model compound (12b*S*)-**16** were calculated by the π-electron SCF-CI-DV MO method.[8-10] In the dipole velocity method, the rotational strength R_{ba} and dipole strength D_{ba} are formulated as follows:

$$R_{ba} = 2(\psi_a|\nabla|\psi_b)(\psi_a|\mathbf{r} \times \nabla|\psi_b)\beta_M{}^2/(\pi\sigma_{ba}) \quad (1)$$

$$D_{ba} = 2(\psi_a|\nabla|\psi_b)^2\beta_M{}^2/(\pi\sigma_{ba})^2 \quad (2)$$

where ∇ is the del operator, $\mathbf{r}$ is a distance vector, β_M is the Bohr magneton, and σ_{ba} is the excitation wavenumber of the transition a $\rightarrow$ b. The *z*-axis component of the electric and magnetic transition moments are expressed, respectively, as[9,10]

$$(\psi_a|\nabla|\psi_b)_z = \sum_{\text{bonds}} (C_{ra}C_{sb} - C_{sa}C_{rb})\langle\nabla_{rs}\rangle \cos Z_{rs} \quad (3)$$

$$(\psi_a|\mathbf{r} \times \nabla|\psi_b)_z = \sum_{\text{bonds}} (C_{ra}C_{sb} - C_{sa}C_{rb})\langle\nabla_{rs}\rangle(X_{rs} \cos Y_{rs} - Y_{rs} \cos X_{rs}) \quad (4)$$

$$\cos Z_{rs} = (Z_r - Z_s)/R_{rs} \quad (5)$$

$$X_{rs} = (X_r + X_s)/2 \quad (6)$$

where C_{ra} is the coefficient of atomic orbital r in the wave function ψ_a, $\langle\nabla_{rs}\rangle$ is the expectation value of a dipole velocity vector ∇_{rs} which is directed along the bond rs in the direction r $\rightarrow$ s, X_r, Y_r, and Z_r are the *x*, *y*, and *z* coordinates of an atom r, respectively, and R_{rs} is the interatomic distance between atoms r and s. In a similar way, the *x* and *y* components of the electric and magnetic transition moments were calculated.

In the π-electron SCF-CI-DV MO calculation, the following standard values of atomic orbital parameters were employed: for sp^2 carbons, $Z(C) = 1.0$, $W(C) = -11.16$ eV, $(rr|rr)(C) = 11.13$ eV, β(C–C, 1.388 Å) = −2.32 eV, $\langle\nabla\rangle$(C–C, 1.388 Å) = 4.70 $\times$ 10^7 cm^{-1}; for ether oxygens, $Z(O) = 2.0$, $W(O) = -33.00$ eV, $(rr|rr)(O) = 21.53$ eV, β(C–O) = −2.00 eV, $\langle\nabla\rangle$(C–O) = 6.00 $\times$ 10^7 cm^{-1}. The electric repulsion integral (rr|ss) was estimated by the Nishimoto–Mataga equation. The resonance integral and del value were calculated by employing the following equations, respectively:

$$\beta = [S/S(1.388\ \text{Å})]\beta(1.388\ \text{Å}) \cos\theta \quad (7)$$

$$\langle\nabla\rangle = [\langle\nabla\rangle(\text{empir}, 1.388\ \text{Å})/\langle\nabla\rangle(\text{theor}, 1.388\ \text{Å})] \times \langle\nabla\rangle(\text{theor}) \cos\theta \quad (8)$$

where θ is a dihedral angle. The overlap integral S and $\langle\nabla\rangle$(theor) were calculated on the basis of the Slater orbitals. The configuration interactions between all singly excited states were included.

The curves of the component CD and UV bands were approximated by the Gaussian distribution

$$\Delta\epsilon(\sigma) = \sum\Delta\epsilon_k \exp[-((\sigma - \sigma_k)/\Delta\sigma)^2] \quad (9)$$

$$\epsilon(\sigma) = \sum\epsilon_k \exp[-((\sigma - \sigma_k)/\Delta\sigma)^2] \quad (10)$$

where $2\Delta\sigma$ is the $1/e$ width of bands. The $\Delta\sigma$ value of 2500 cm^{-1} was adopted as a standard value.

Numerical calculations were carried out on the NEC ACOS-2000 computer at the Computer Center of Tohoku University.

Results and Discussion

Attempt of the Application of the π-Electron SCF-CI-DV MO Method to Halenaquinol Dimethyl Ether. To determine the absolute configuration of halenaquinol **2**, we at first tried to apply the π-electron SCF-CI-DV MO method to halenaquinol dimethyl ether **7**, because halenaquinol dimethyl ether has the conjugated π-electron system composed of a naphthalene–ketone–furan–ketone chromophore which is twisted by the only chiral center of the angular methyl group at the 12b position. In this case, halenaquinol itself was not employed, because halenaquinol is fairly unstable for light and heat (even at 40 °C). Furthermore, as a protection group, we preferred methyl ether rather than acetate, because the π-electron system of dimethyl ether **7**, which contains the lone-pair electrons of ether oxygens, is much simpler than that of halenaquinol diacetate. In the latter case, the π-electron system becomes more complex due to the contribution of the ester carbonyl moieties.

Halenaquinol **2** was methylated in refluxing acetone with iodomethane in the presence of potassium carbonate in the dark yielding dimethyl ether (+)-**7** as yellow needles (Scheme I): mp 235 °C; $[\alpha]^{23}_D$ +150.1° (CH_2Cl_2).[16,17] Although we anticipated

(13) Harada, N.; Kohori, J.; Uda, H.; Nakanishi, K.; Takeda, R. *J. Am. Chem. Soc.* **1985**, *107*, 423. Harada, N.; Kohori, J.; Uda, H.; Toriumi, K. *J. Org. Chem.* **1989**, *54*, 1820.
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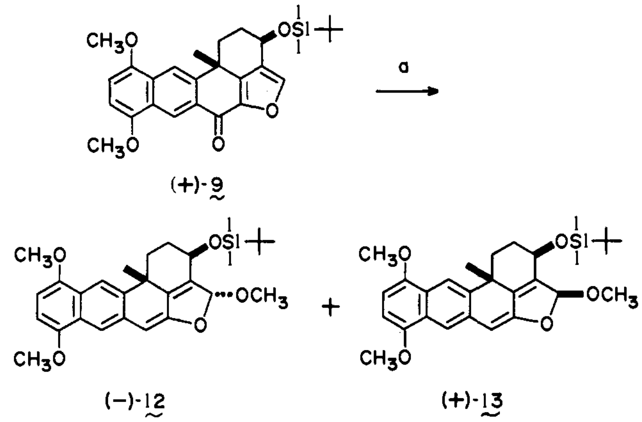
(15) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. Allinger, N. L.; Yuh, Y. H. *QCPE* **1980**, *12*, 395.

Scheme II[a]



[a](a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, CH_2Cl_2, and then aqueous HCl.

the relatively intense CD Cotton effects for **7**, the CD spectrum showed weak Cotton effects as described in the Experimental Section. The weak intensity of the CD Cotton effects may be due to the existence of two carbonyl groups of strong electron-withdrawing nature, which makes the total π-electron system to be less symmetrical and hence the electronic transitions to be more complex and weaker, as observed in the case of 2,2′-spirobi[2*H*-benz[*e*]indene]-1,1′(3*H*,3′*H*)-dione.[18] Therefore, from the view point of the reliability of the determination, the CD data of **7** were not useful for the theoretical determination of the absolute configuration, because it is a rather difficult work to discriminate small positive and negative $\Delta\epsilon$ values. In fact, we actually performed the theoretical calculation of the CD spectrum of **7**, and the obtained results seemed to lead to the 12b*S* absolute configuration for (+)-**7**. However, we could not come to the convincing and unambiguous assignment of the absolute configuration because of the small $\Delta\epsilon$ values.

Attempt of the Application of the CD Exciton Chirality Method. As a second strategy, we planned to synthesize benzoate derivative **11** and to apply the CD exciton chirality method[10] to the interaction between the naphthalene and benzoate chromophores of compound **11** (Scheme I). There are many examples of the exciton interaction between the ^1B_b transition of a naphthalene chromophore and the intramolecular CT or ^1L_a transition of a benzoate chromophore. So, the applicability of the CD exciton chirality method to such a system has been already established.[10]

To differentiate the two carbonyl groups at the 3- and 6-positions, halenaquinol dimethyl ether **7** was selectively reduced with $NaBH_4$ in the presence of $CeCl_3{\cdot}7H_2O$, which catalyzes the regioselective 1,2-reduction of conjugated enones (Scheme I).[19] Keto-alcohol (+)-**8** was obtained as yellow needles, mp 258–259 °C, and its structure was secured by the ^1H NMR coupling constant data. The alcohol was then converted to *tert*-butyldimethylsilyl ether (+)-**9**: mp 220–221 °C. To reduce the carbonyl group at the 6-position, keto-silyl ether **9** was treated with $NaBH_4/CeCl_3{\cdot}7H_2O$ in methanol/dichloromethane. However, the obtained product which was postulated as alcohol **10** was extremely unstable and could not be isolated. So, the introduction of a benzoate chromophore at the 6-position and the application of the exciton chirality method were unfortunately unsuccessful.

Application of the π-Electron SCF-CI-DV MO Method to Naphthalene-Diene Derivatives. Although we have failed to obtain alcohol **10**, it was very lucky, as discussed below, that the reductive reaction of ketone **9** discussed above gave the rearranged products **12** and **13** instead of **10** (Scheme II). These compounds are considered to be derived from alcohol **10**, which undergoes the elimination of the hydroxyl group and simultaneous addition of methanol at the 4-position at the stage of working up. In fact, the reduction of ketone **9** and subsequent treatment of the reaction mixture with a catalytic amount of aqueous hydrochloric acid afforded trans-methoxy diene (−)-**12** and cis-methoxy diene (+)-**13** as yellow amorphous materials, respectively, in a moderate yield (Scheme II). The structures of acetal epimers **12** and **13** were secured by the spectroscopic data; especially the relative stereochemistries were unambiguously determined by the ^1H NMR coupling constant and NOE enhancement data listed in the Experimental Section and illustrated in Figure 1.

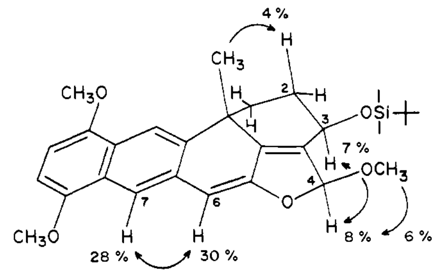
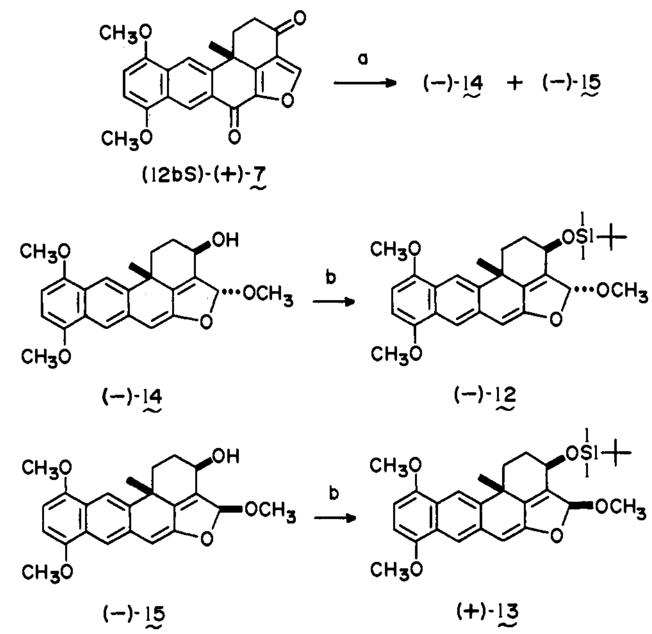


Figure 1. ^1H NMR NOE enhancement data corroborating the relative stereochemistry of (3*R*,4*S*,12b*S*)-(+)-**13** (in benzene-d_6).

Scheme III[a]



[a](a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, CH_2Cl_2, and then aqueous HCl; (b) *tert*-Butylchlorodimethylsilane, imidazole, DMF.

The naphthalene-diene compounds **12** and **13** were also derived directly from halenaquinol dimethyl ether **7** by the reduction and subsequent *tert*-butyldimethylsilylation (Scheme III). Diketone **7** was reduced and treated with hydrochloric acid, as in the case of ketone **9** of Scheme II, giving trans-methoxy alcohol (−)-**14** and cis-methoxy alcohol (−)-**15** as solid materials, respectively. Each alcohol was converted to its *tert*-butyldimethylsilyl ether, which was identical with the authentic sample derived from compound **9**.

By the reactions discussed above, four naphthalene-diene compounds (−)-**12**, (+)-**13**, (−)-**14**, and (−)-**15** were obtained. It was quite surprising that these naphthalene-diene compounds exhibited much stronger CD Cotton effects than any other halenaquinol derivatives, as listed in Table I. For example, trans-methoxysilyl ether (−)-**12** shows two intense $\pi \rightarrow \pi^*$ UV bands (Figure 2): the broad band at 324 nm (ϵ 27 000) with complicated vibrational structures and the sharp band at 218 nm (ϵ 42 000). In the corresponding region, the CD spectrum of **12** exhibits three major intense Cotton effects: λ_{ext} 338 nm ($\Delta\epsilon$ +6.4), 301 nm ($\Delta\epsilon$

(16) All of the new compounds have been characterized by spectroscopic methods including high-resolution mass spectrometry.

(17) Reinvestigation of the $[\alpha]_D$ value of **7** gave the larger value than that reported in ref 6.

(18) Harada, N.; Iwabuchi, J.; Yokota, Y.; Uda, H. *Croat. Chem. Acta*, in press.

(19) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

Table I. Calculated and Observed UV and CD Spectra of the Naphthalene-Diene Derivatives of Halenaquinol (Observed in Methanol)

compd	UV, λ_{max},[a] nm (ε)	CD λ_{ext},[a] nm (Δε)
model (12b*S*)-**16** (calcd)		*378 (+3.3)*
	349 (29 900)	
		322 (−22.4)
		248 (−5.7)
		223 (+35.5)
	219 (40 300)	
(−)-**12** (obsd)	382 (8 000)	
	367 (10 000)	
	339 (26 000)	*338 (+6.4)*
	324 (27 000)	326 (+0.6)
	314 sh (23 000)	
		301 (−23.3)
	283 (25 000)	
	277 sh (24 000)	
	258 sh (10 000)	255 (+1.2)
		248 (−1.5)
		229 (+40.9)
	218 (42 000)	
(+)-**13** (obsd)	383 (8 000)	
	367 (11 000)	
	342 (26 000)	*341 (+6.1)*
		329 (+0.9)
	326 (26 000)	325 (+1.2)
	314 sh (22 000)	
		302 (−15.8)
	284 (24 000)	
	277 sh (22 000)	
	259 sh (10 000)	257 (+1.8)
		248 (−0.9)
		231 (+29.4)
	218 (41 000)	
(−)-**14** (obsd)	383 sh (7 000)	
	367 (9 000)	
	339 (22 000)	*339 (+6.4)*
	324 (22 000)	326 (+0.6)
	315 sh (20 000)	
		301 (−18.5)
	283 (21 000)	
	278 sh (20 000)	
	259 sh (8 000)	256 (+1.5)
		247 (−0.6)
	229 sh (24 000)	*229 (+33.3)*
	218 (37 000)	
(−)-**15** (obsd)	383 sh (8 000)	
	368 (10000)	
	341 (24 000)	*341 (+6.4)*
	326 (24 000)	327 (+1.5)
	315 sh (22 000)	
		303 (−16.1)
	285 (20 000)	
	279 sh (19 000)	
	261 sh (7 000)	
		256 (+1.5)
		247 (−1.2)
	230 sh (24 000)	*230 (+30.6)*
	219 (37 000)	

[a] Data in italics indicate the major UV and CD bands.

−23.3), and 229 nm (Δε +40.9). The remaining three naphthalene-diene compounds also show three major CD Cotton effects of similar intensity and of the same sign as those of **12** (Table I). These results clearly indicate that the major part of the CD Cotton effects originates from the π-electron chromophore composed of the naphthalene-diene moiety which is twisted by the angular methyl group at the 12b position. Namely, the additional chiralities due to the silyloxy group at the 3-position and the methoxy group at the 4-position are less contributory to the CD Cotton effects. In other words, these naphthalene-diene compounds are ideal systems for the determination of the absolute stereochemistry by the application of the π-electron SCF-CI-DV MO method.

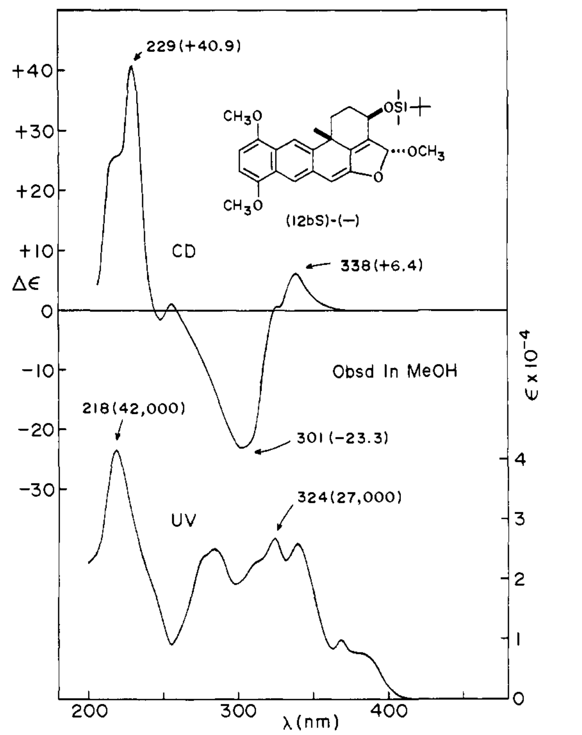
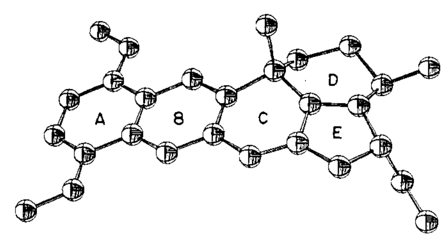
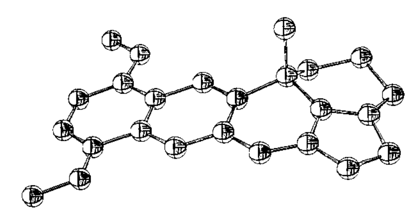


Figure 2. Observed CD and UV spectra of halenaquinol trans-methoxy diene derivative (3*R*,4*R*,12b*S*)-(−)-**12** in methanol.



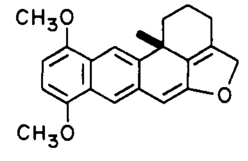
(3R,4R,12bS)-(−)-14



(12bS)-16

Figure 3. Stereoscopic view of halenaquinol trans-methoxy diene derivative (3*R*,4*R*,12b*S*)-(−)-**14** and the model compound (12b*S*)-**16** calculated by the molecular mechanics.

As a model compound for the theoretical calculation of CD spectra, we adopted the molecule **16**, which has the essential part



(12bS)-16

of the π-electron system of naphthalene-diene compounds **12**–**15**. Namely, in addition to the naphthalene and conjugated diene chromophores, the lone-pair electrons of the two methyl ether and furan oxygens are also included. The absolute configuration of **16** was arbitrarily chosen to be 12b*S* for the calculation. The

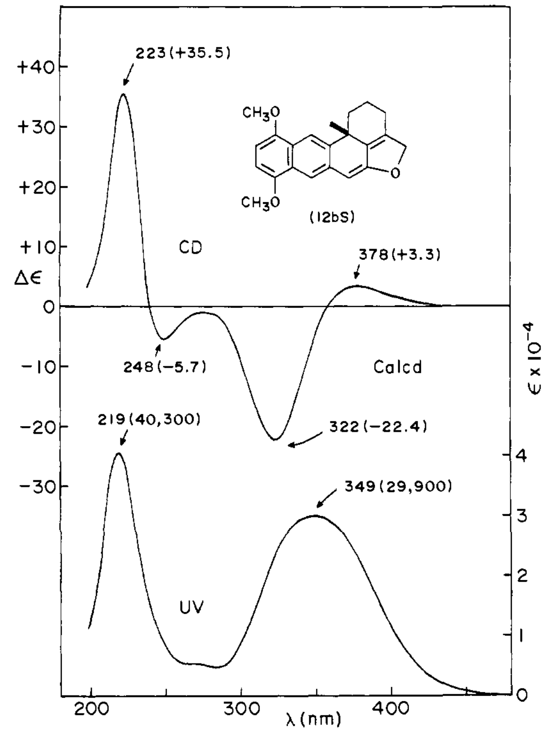


Figure 4. CD and UV curves of the model compound (12b*S*)-**16** calculated by the π-electron SCF-CI-DV MO method.

molecular geometry of the model compound was calculated by the molecular mechanics (MMP2)[15] as illustrated in Figure 3, where the geometry of (3*R*,4*R*,12b*S*)-**14** is also shown. The molecular framework of these compounds is relatively rigid, and the D ring takes a half-chair conformation. These molecular conformations were secured by the ^1H NMR coupling constant and NOE enhancement data of compounds (+)-**13** and (−)-**15** (Figure 1 and Experimental Section). The double bond and naphthalene chromophores make a clockwise helicity (dihedral angle of 5a–6–6a–7: +170° for **16**, +171° for **14**) for the 12b*S* absolute configuration, while the conjugated diene moiety constitutes a counterclockwise helicity (dihedral angle of 3a–12c–5a–6: −167° for **16**, −168° for **14**). The helical sense of these two moieties is not changed, even if the D ring takes a boat conformation. Namely, the sense of the twist of the conjugated π-electron system is governed solely by the chirality of the angular methyl group at the 12b position.

The theoretical calculation of the CD and UV spectra of (12b*S*)-**16** by the π-electron SCF-CI-DV MO method afforded the curves illustrated in Figure 4. The UV spectrum curve exhibits two intense $\pi \rightarrow \pi^*$ bands: a broad band at 349 nm (ε 29 900) and a sharp band at 219 nm (ε 40 300). These calculated values agree closely with the observed UV data of (−)-**12** and other naphthalene-diene derivatives (Table I): for **12**, λ_{max} 324 nm (ε 27 000) and 218 nm (ε 42 000) (Figure 2). In the corresponding region, the CD calculation yielded three principal Cotton effects: a weak positive band at 378 nm (Δε +3.3), a negative one of medium intensity at 322 nm (Δε −22.4), and a positive intense one at 223 nm (Δε +35.5). These theoretically obtained CD values are also in a good agreement with the observed data of (−)-**12** and other naphthalene-diene compounds (Table I): for **12**, λ_{ext} 338 nm (Δε +6.4), 301 nm (Δε −23.3), and 229 nm (Δε +40.9) (Figure 2). It is thus evident that the basic pattern of the CD and UV spectral curves, including the sign, position, intensity, and shape of the bands, was well reproduced by the calculation. Since the absolute configuration of the model compound **16** is fixed to be 12b*S*, the comparison of the present calculated and observed data leads to the unambiguous determination that the naphthalene-diene compounds **12–15** have the 12b*S* absolute configuration. Accordingly, the absolute stereochemistry of halenaquinol (+)-**2** was theoretically determined to be 12b*S*. Since the UV irradiation of halenaquinol (+)-**2** gave halenaquinone (+)-**1** and the solvolysis of halenaquinol sulfate (+)-**3** furnished halenaquinol (+)-**2** quantitatively, the absolute stereostructures of **1** and **3** were also established to be 12b*S*, respectively.

Table II. Calculated Dipole and Rotational Strengths of the Transitions of the Naphthalene-Diene Model Compound (12b*S*)-**16**

wavelength (λ), nm	dipole strength ($10^{36}D$), cgs unit	rotational strength ($10^{40}R$), cgs unit
374.5	23.1	+8.3
351.6	18.9	+15.3
324.4	24.0	−79.6
243.3	5.1	−12.3
235.1	4.3	−21.4
226.6	8.9	+83.4
219.9	13.7	−3.3
217.3	12.2	+18.4
208.2	6.8	+18.4

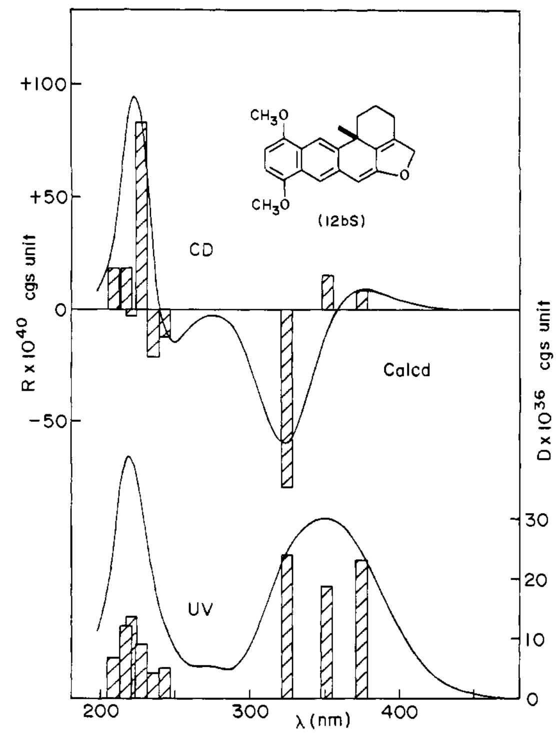


Figure 5. Rotational and dipole strengths of the transitions of the model compound (12b*S*)-**16** calculated by the π-electron SCF-CI-DV MO method.

Circular Dichroic Power of a Twisted Naphthalene-Diene System. In the case of (8a*S*)-(+)-1,8a-dihydroazulene previously reported,[13] the composition of the apparent CD and UV bands was rather simple, because each of the apparent bands was composed of a single electronic transition. The case of chiral troponoid spiro compounds was also rather simple because of their C_2 symmetric structures.[14] On the other hand, the present π-electron chromophore is totally complex and has no symmetric character. So, to clarify the applicability of the present theoretical method to such a complicated system, it is significant to analyze the composition of the apparent CD and UV bands. As shown in Table II and Figure 5, there are nine major electronic transitions that contribute to the CD and UV bands. The first and second transitions with weak positive rotational strengths at 374.5 and 351.6 nm, respectively, generate the weak positive Cotton effect at 378 nm (Figure 5). Furthermore, the third transition with an intense negative rotational strength at 324.4 nm results in the negative Cotton effect at 322 nm, and the sixth transition with a strong positive rotational strength contributes mainly to the intense positive Cotton effect at 223 nm. The correspondence between the component transitions and the apparent CD bands is thus unambiguous. Therefore, the present analysis makes the absolute configurational determination of the halenaquinol compounds to be more reliable.

Cardiotonic Activity of Halenaquinol. Ohizumi and co-workers reported that xestoquinone **4** showed a marked cardiotonic activity.[4] So, halenaquinol **2** and halenaquinol sulfate **3** were also subjected to the biological activity tests. Although halenaquinol sulfate showed almost no activity, halenaquinol itself showed a strong inotropic effect on the isolated guinea pig left atria (ED_{50} 6×10^{-7} M) which is comparable to that of xestoquinone (ED_{50} 2×10^{-6} M). Furthermore, halenaquinol caused an inhibitory effect on the cyclic AMP phosphodiesterase from bovine heart (IC_{50} 4×10^{-6} M). Therefore, it is probable that the increase of the cyclic AMP caused by the inhibition of phosphodiesterase results in the cardiotonic activity.

Concluding Remarks

The absolute stereostructures of halenaquinone (+)-**1**, halenaquinol (+)-**2**, and halenaquinol sulfate (+)-**3**, novel pentacyclic marine natural products isolated from tropical marine sponges, were theoretically determined to be 12b*S*, respectively, on the basis of the calculation of the CD spectra of naphthalene-diene derivatives by the π-electron SCF-CI-DV MO method. The present studies also clarified that the theoretical CD method was applicable to such complex natural products. The conclusions theoretically obtained are consistent with the results of the experimental determination of their absolute configurations by the total synthesis of halenaquinone and halenaquinol of natural enantiomeric forms.[7] Therefore, the present methodology would become a promising tool for the determination of the absolute stereochemistry of various complex natural products with a twisted π-electron system.[21]

Experimental Section

General Procedures. Melting points were taken on a Yanagimoto micro-melting-point apparatus and are uncorrected. IR spectra were obtained as KBr disks or $CHCl_3$ solutions by using a Hitachi 260-30 spectrophotometer. ^1H NMR spectra were recorded on a JEOL FX90Q (90 MHz) or a JEOL JNM FX-500S (500 MHz) spectrometer. ^{13}C NMR spectra were obtained on a JEOL FX90Q (22.5 MHz). All NMR data are reported in ppm (δ) downfield from tetramethylsilane. The abbreviations (S, D, T, Q, etc.) given in the ^{13}C NMR data denote the coupling patterns arising from the directly bonded protons. Optical rotation $[\alpha]_D$ measurements were made on a JASCO DIP-181 spectropolarimeter. UV and CD spectra were recorded on a Hitachi 330 spectrophotometer and on a JASCO J-500A spectropolarimeter with a DP-501 data processor, respectively. Mass spectra were obtained with a JEOL D-300 spectrometer by the electron ionization procedure (70 eV), unless otherwise noted.

Halenaquinone (1):[2] yellow solid; UV (MeOH) λ_{max} 317 nm (ϵ 6900), 305 sh (7100), 293 sh (7400), 265 sh (13 400), 245 (18 700), 222 (31 600); CD (MeOH) λ_{ext} 216 nm ($\Delta\epsilon$ +2.8).

Halenaquinol (2): yellow amorphous; IR (KBr) ν_{max} 3360 (br), 1685 (sh), 1656, 1627, 1611, 1592, 1522, 1440, 1291, 1238, 1143, 1114, 1016 cm^{-1}; ^1H NMR (90 MHz, DMSO-d_6) δ 1.65 (3 H, s, 12b-CH_3), 2.29 (1 H, m), 2.5–3.0 (3 H, m), 6.87 (1 H, d, J = 8.0 Hz, 9-H or 10-H), 6.97 (1 H, d, J = 8.0 Hz, 10-H or 9-H), 8.31 (1 H, s, 12-H), 8.75 (1 H, s, 4-H), 9.04 (1 H, s, 7-H); ^{13}C NMR (22.5 MHz, DMSO-d_6) δ 31.9 (Qm, 12b-CH_3), 33.7 (Tm, C-1), 35.6 (Sm, C-12b), 36.7 (Tm, C-2), 109.0 (Dd, C-10 or C-9), 112.0 (Dd, C-9 or C-10), 119.0 (Ds, C-12), 122.4 (Sd, C-3a), 123.5 (Sq, C-7a), 124.1 (Ds, C-7), 126.5 (Sq, C-11a), 129.5 (Sd, C-6a), 143.7 (Sm, C-12c), 144.9 (Sd, C-5a), 145.3 (Sm, C-11), 147.3 (Sm, C-8), 147.7 (Sm, C-12a), 150.0 (Ds, C-4), 172.2 (Sd, C-6), 192.3 (Sm, C-3); $[\alpha]_{577}$ +179° (acetone); UV (MeOH) λ_{max} 431 nm (ϵ 4200), 302 (23 000), 284 sh (20 000), 228 (36 000); CD (MeOH) λ_{ext} 345 nm ($\Delta\epsilon$ +2.8), 244 (+6.4), 229 (−4.5); MS (EI) m/z 334 (parent, relative intensity 56%), 319 (100). High-resolution mass spectrum: calcd for $C_{20}H_{14}O_5$, 334.084; found: 334.081.

Halenaquinol sulfate (3): brown amorphous; IR (KBr) ν_{max} 3450 (br), 1661, 1632, 1262, 1244, 1052, 1029, 1013 cm^{-1}; ^1H NMR (90 MHz, DMSO-d_6) δ 1.67 (3 H, s, 12b-CH_3), 2.2–2.8 (4 H, m), 6.92 (1 H, d, J = 8.0 Hz, 9-H), 7.49 (1 H, d, J = 8.0 Hz, 10-H), 8.38 (1 H, s, 12-H), 8.75 (1 H, s, 4-H), 9.04 (1 H, s, 7-H); ^{13}C NMR (22.5 MHz, DMSO-d_6) δ 31.7 (Qm, 12b-CH_3), 33.8 (Tm, C-1), 35.7 (Sm, C-12b), 36.5 (Tm, C-2), 108.4 (Dd, C-9), 120.3 (Ds, C-12), 121.6 (Ds, C-10), 122.4 (Sd, C-3a), 123.4 (Sq, C-7a), 123.9 (Ds, C-7), 129.5 (Sd, C-6a), 130.0 (St, C-11a), 141.1 (Sm, C-11), 144.5 (Sm, C-12c), 144.8 (Sd, C-5a), 147.8 (Sm, C-12a), 150.4 (Ds, C-4), 151.4 (Sm, C-8), 172.0 (Sd, C-6), 192.3 (Sm, C-3); $[\alpha]_{577}$ +106° (MeOH); UV (MeOH) λ_{max} 398 nm (ϵ 6400), 318 sh (12 000), 296 (22 000), 275 (20 000), 225 (41 000); CD (MeOH) λ_{ext} 301 nm ($\Delta\epsilon$ −4.8), 244 (+3.3), 230 (−11.5), 213 (+9.1); secondary ion MS (glycerol) m/z 551 (M + Na + glycerol), 529 (M + H + glycerol), 459 (M + Na), 437 (M + H). Anal. Calcd for $C_{20}H_{13}NaO_8S{\cdot}3H_2O$: C, 49.0; H, 3.9; S, 6.5. Found: C, 49.0; H, 3.6; S, 6.4.

(+)-Halenaquinol Dimethyl Ether 7. To a solution of halenaquinol (**2**, 0.295 g) in acetone (4 mL) were added anhydrous potassium carbonate (0.360 g) and iodomethane (1.2 mL) under nitrogen. After being gently refluxed in the dark for 14 h, the reaction mixture was diluted with ethyl acetate (50 mL) and then filtered. The filtrate was washed successively with 2 M HCl, aqueous $NaHCO_3$, and brine and then dried over anhydrous $MgSO_4$. Evaporation of the solvent in vacuo gave a crude product which was purified by a chromatography on silica gel (hexane-/EtOAc 2:1) affording halenaquinol dimethyl ether **7** (0.168 g, 53%) as yellow needles: mp 234–235 °C (hexane/EtOAc); IR ($CHCl_3$) ν_{max} 2943, 1698, 1674, 1632, 1600 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$)[20] δ 1.67 (3 H, s, 12b-CH_3), 2.33 (1 H, m), 2.83–3.07 (3 H, m), 3.98 (6 H, s, OCH_3), 6.72 (1 H, d, J = 8.5 Hz, 9-H or 10-H), 6.83 (1 H, d, J = 8.5 Hz, 10-H or 9-H), 8.21 (1 H, s, 4-H), 8.29 (1 H, s, 12-H), 9.27 (1 H, s, 7-H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 31.6 (Q, 12b-CH_3), 34.1 (T, C-1), 35.7 (S, C-12b), 36.7 (T, C-2), 55.6 (Q, 8-OCH_3 and 11-OCH_3), 103.8 (D, C-9 or C-10), 106.5 (D, C-10 or C-9), 118.3 (D, C-12), 122.4 (S, C-3a), 124.4 (D, C-7), 124.7 (S, C-7a), 127.5 (S, C-11a), 130.4 (S, C-6a), 144.3 (S, C-5a), 145.6 (S, C-12c), 146.9 (S, C-11), 148.1 (D, C-4), 148.6 (S, C-8), 150.7 (S, C-12a), 172.4 (S, C-6), 191.9 (S, C-3); $[\alpha]^{23}_D$ +150.1° (c 1.124, CH_2Cl_2);[17] UV (MeOH) λ_{max} 409 nm (ϵ 5000), 299 (24 000), 282 sh (19 000), 226 (40 000); CD (EtOH) λ_{ext} 413 nm ($\Delta\epsilon$ +1.8), 383 (+1.4), 363 (+1.7), 347 (+2.8), 303 (−5.5), 244 (+4.6), 232 (−8.9); MS m/z 362 (parent, 91), 347 (100), 332 (21), 317 (24). High-resolution mass spectrum: calcd for $C_{22}H_{18}O_5$, 362.115; found, 362.116.

(+)-Keto-Alcohol 8. To a solution of halenaquinol dimethyl ether **7** (0.060 g) in dichloromethane (5 mL) and methanol (5 mL) was added $CeCl_3{\cdot}7H_2O$ (0.600 g).[19] After the mixture was stirred at room temperature for 10 min, $NaBH_4$ (0.007 g) was added. After being stirred for 10 min, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The crude product obtained was purified by a column chromatography on silica gel (hexane-/EtOAc 1:1) and by an HPLC (Zorbax ODS, MeOH/H_2O 8:1) to yield alcohol **8** (0.027 g, 44%) as yellow needles: mp 258–259 °C (hexane/EtOAc); IR (KBr) ν_{max} 3400 (br), 2930, 1658, 1625, 1610 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.63 (3 H, s, 12b-CH_3), 2.1–3.1 (4 H, m), 3.99 (6 H, s, OCH_3), 5.00 (1 H, dd, J = 8.0 and 8.0 Hz, 3α-H), 6.72 (1 H, d, J = 8.5 Hz, 9-H or 10-H), 6.83 (1 H, d, J = 8.5 Hz, 10-H or 9-H), 7.78 (1 H, d, J = 2.0 Hz, 4-H), 8.23 (1 H, s, 12-H), 9.27 (1 H, s, 7-H); $[\alpha]^{23}_D$ +82° (c 0.3, acetone); UV (MeOH) λ_{max} 405 nm (ϵ 4000), 309 (16 000), 281 (12 000), 225 (30 000); CD (MeOH) λ_{ext} 406 nm ($\Delta\epsilon$ +1.8), 344 (+4.6), 307 (−5.8), 283 (+1.8), 239 (−11.8), 217 (+13.6); MS m/z 364 (parent, 100), 349 (43), 331 (67). High-resolution mass spectrum: calcd for $C_{22}H_{20}O_5$, 364.130; found, 364.131.

(+)-Keto-Silyl Ether 9. To a solution of keto-alcohol **8** (0.019 g) in *N,N*-dimethylformamide (DMF, 1 mL) were added *tert*-butylchlorodimethylsilane (0.060 g) and imidazole (0.044 g). After being stirred under nitrogen at room temperature for 20 min, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and then evaporated in vacuo. The residue obtained was chromatographed on silica gel (hexane/EtOAc 6:1) affording silyl ether **9** (0.019 g, 77%) as yellow needles: mp 220–221 °C (hexane/EtOAc); IR ($CHCl_3$) ν_{max} 2950, 1666, 1628, 1613, 1461 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.20 (6 H, s), 0.98 (9 H, s), 1.63 (3 H, s, 12b-CH_3), 2.0–2.9 (4 H, m), 3.99 (6 H, s, OCH_3), 4.95 (1 H, m, 3-H), 6.71 (1 H, d, J = 8.5 Hz, 9-H or 10-H), 6.82 (1 H, d, J = 8.5 Hz, 10-H or 9-H), 7.62 (1 H, d, J = 2.0 Hz, 4-H), 8.22 (1 H, s, 12-H), 9.26 (1 H, s, 7-H); ^{13}C NMR (22.5 MHz, benzene-d_6) δ −4.4 (Si–C), −4.3 (Si–C), 18.2 (Si–C), 26.0 (Si–C(CH_3)$_3$), 31.7 (Tm, C-1), 32.9 (Tm, C-2), 34.6 (Qm, 12b-CH_3), 36.2 (Sm, C-12b), 55.4 (Q, 8- and 11-OCH_3), 63.7 (Dm, C-3), 103.7 (Ds, C-9 or C-10), 106.3 (Ds, C-10 or C-9), 117.8 (Ds, C-12), 124.2 (Ds, C-7), 125.0 (St, C-7a), 125.9 (Sbr d, C-3a), 127.7 (St, C-11a), 132.0 (Sd, C-6a), 145.3 (Sd, C-5a), 145.3 (Dd, C-4), 146.2 (Sm, C-12c), 146.6 (Sm, C-11), 149.1 (Sm, C-8 or C-12a), 150.9 (Sm, C-12a or C-8), 172.3 (Sd, C-6); $[\alpha]^{24}_D$ +136° (c 0.2, benzene); UV (MeOH) λ_{max} 407 nm (ϵ 5000), 323 sh (16 000), 308 (21 000), 281 (17 000), 225 (38 000); CD (MeOH) λ_{ext} 344 nm ($\Delta\epsilon$ +5.6), 307 (−6.2), 283 (+2.6), 255 sh (−3.4), 240 (−11.7), 218 (+16.5);

(20) For the details of the NMR data and assignments, see ref 7.

(21) The absolute stereochemistry of xestoquinone (+)-**4** was recently determined to be 12b*S* by the total synthesis of (+)-**4**: Harada, N.; Sugioka, T.; Uda, H.; Kuriki, T., 58th Annual Meeting of the Chemical Society of Japan, Kyoto, April 1989, Abstract II, page 1234, 11M35.

MS m/z 478 (parent, 37), 331 (67). High-resolution mass spectrum: calcd for $C_{28}H_{34}O_5Si$, 478.217; found, 478.217.

Diene-Silyl Ethers (−)-12 and (+)-13. To a solution of keto-silyl ether **9** (0.049 g) in dichloromethane (1 mL) and methanol (1 mL) was added $CeCl_3 \cdot 7H_2O$, and the mixture was stirred at room temperature for 5 min. Sodium borohydride (0.100 g) was added, and then the mixture was further stirred for 10 min. After a check of the disappearance of the starting material on thin-layer chromatography (TLC, silica gel, hexane/EtOAc 3:1), the reaction mixture was treated with an aqueous HCl solution (1 M, 0.050 mL) and stirred for additional 30 min. The mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine and evaporated in vacuo to dryness. The crude products obtained were separated and purified by a column chromatography on silica gel (hexane/EtOAc 3:2) and by an HPLC (Zorbax ODS, $MeOH/H_2O$ 30:1) affording two diene compounds **12** (0.018 g, 35%) and **13** (0.010 g, 20%).

Trans-methoxy diene **12**: yellow amorphous; IR ($CHCl_3$) ν_{max} 2930, 1650, 1598, 1458, 1089 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 0.08 (3 H, s, $SiCH_3$), 0.10 (3 H, s, $SiCH_3$), 0.99 (9 H, s, $SiC(CH_3)_3$), 1.35 (3 H, s, 12b-CH_3), 1.85 (1 H, ddd, J = 13.5, 12.0, 5.0 Hz, 1 ax-H), 1.9–2.1 (2 H, m, 2-H), 2.16 (1 H, ddd, J = 13.5, 3.5, 3.0 Hz, 1 eq-H), 3.29 (3 H, s, 4-OCH_3), 3.53 (3 H, s, 8-OCH_3 or 11-OCH_3), 3.59 (3 H, s, 11-OCH_3 or 8-OCH_3), 4.60 (1 H, dd, J = 8.0, 8.0 Hz, 3 ax-H), 6.11 (1 H, s, 6-H), 6.22 (1 H, s, 4-H), 6.41 (1 H, d, J = 8.0 Hz, 9-H or 10-H), 6.42 (1 H, d, J = 8.0 Hz, 10-H or 9-H), 8.20 (1 H, s, 7-H), 8.25 (1 H, s, 12-H); ^{13}C NMR (22.5 MHz, benzene-d_6) δ −4.9 (Si–C), −4.3 (Si–C), 18.2 (Si–C), 26.0 ($SiC(CH_3)_3$), 32.2 (Tm, C-1), 32.5 (Qm, 12b-CH_3), 34.7 (Tm, C-2), 36.9 (Sm, C-12b), 55.3 (Q, 8-OCH_3 and 11-OCH_3), 55.6 (Q, 4-OCH_3), 65.6 (Dm, C-3), 99.0 (Dm, C-4), 102.9 (Ds, C-9 or C-10), 103.6 (Ds, C-10 or C-9), 111.4 (Dd, C-6), 117.4 (Ds, C-12), 119.9 (Dd, C-7), 124.9 (St, C-7a), 126.5 (St, C-11a), 133.7 (Sd, C-6a), 135.7 (Sm, C-12a), 140.6 (Sm, C-12c), 143.2 (Sm, C-3a), 149.9 (St, C-8 and C-11), 158.4 (Sd, C-5a); $[\alpha]^{24}{}_D$ −151° (c 0.1, benzene); MS m/z 494 (parent, 100), 448 (11), 422 (43). High-resolution mass spectrum: calcd for $C_{29}H_{38}O_5Si$, 494.249; found, 494.250.

Cis-methoxy diene **13**: yellow amorphous; IR ($CHCl_3$) ν_{max} 2930, 1648, 1598, 1459, 1101 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 0.05 (3 H, s, Si-CH_3), 0.09 (3 H, s, Si-CH_3), 1.00 (9 H, s, $SiC(CH_3)_3$), 1.31 (3 H, s, 12b-CH_3), 1.82 (1 H, ddd, J = 13.5, 12.0, 3.0 Hz, 1 ax-H), 1.93 (1 H, dddd, J = 13.0, 8.0, 3.5, 3.0 Hz, 2 eq-H), 2.00 (1 H, dddd, J = 13.0, 12.0, 8.0, 3.0 Hz, 2 ax-H), 2.18 (1 H, ddd, J = 12.5, 3.5, 3.0 Hz, 1 eq-H), 3.28 (3 H, s, 4-OCH_3), 3.55 (3 H, s, 8-OCH_3 or 11-OCH_3), 3.60 (3 H, s, 11-OCH_3 or 8-OCH_3), 4.12 (1 H, dd, J = 8.0, 8.0 Hz, 3 ax-H), 5.90 (1 H, s, 4-H), 6.08 (1 H, s, 6-H), 6.42 (1 H, d, J = 8.0 Hz, 9-H or 10-H), 6.44 (1 H, J = 8.0 Hz, 10-H or 9-H), 8.24 (1 H, s, 7-H), 8.29 (1 H, s, 12-H); NOE experiment (benzene-d_6), see Figure 1; ^{13}C NMR (22.5 MHz, benzene-d_6) δ −4.6 (Si–C), −4.4 (Si–C), 18.3 (Si–C), 26.0 (Si–$C(CH_3)_3$), 32.2 (Tm, C-1), 32.6 (Qm, 12b-CH_3), 34.7 (Tm, C-2), 37.0 (Sm, C-12b), 51.3 (Q, 4-OCH_3), 55.2 (Q, 8-OCH_3 and 11-OCH_3), 66.7 (Dm, C-3), 97.6 (Dm, C-4), 102.8 (Ds, C-9 or C-10), 103.6 (Ds, C-10 or C-9), 110.2 (Dd, C-6), 117.4 (Ds, C-12), 119.6 (Dd, C-7), 124.8 (St, C-7a), 126.4 (St, C-11a), 133.6 (Sd, C-6a), 134.7 (Sm, C-12a), 140.2 (Sm, C-12c), 144.0 (Sm, C-3a), 149.8 (St, C-8 and C-11), 156.8 (Sd, C-5a); $[\alpha]^{24}{}_D$ +20° (c 0.3, benzene); MS m/z 494 (parent, 100), 422 (45). High-resolution mass spectrum: calcd for $C_{29}H_{38}O_5Si$, 494.249; found: 494.250.

Diene-Alcohols (−)-14 and (−)-15. To a solution of halenaquinol dimethyl ether **7** (0.168 g) in dichloromethane (20 mL) and methanol (50 mL) was added $CeCl_3 \cdot 7H_2O$ (1.50 g), and the mixture was stirred at room temperature for 10 min. Sodium borohydride (0.050 g) was added, and the mixture was further stirred for 1 h. After a check of the disappearance of the starting material on TLC (silica gel, hexane/EtOAc 1:1), the reaction mixture was treated with an aqueous HCl solution (2 M, 0.050 mL) and stirred for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine and evaporated in vacuo to dryness. The crude products obtained were separated and purified by a column chromatography on silica gel (hexane/EtOAc 1:1) and by an HPLC (Zorbax ODS, $MeOH/H_2O$ 4:1) giving trans-methoxy diene **14** (0.082 g, 44%) and cis-methoxy diene **15** (0.039 g, 20%).

Trans-methoxy diene **14**: colorless amorphous; IR ($CHCl_3$) ν_{max} 3605, 3420 (br), 2938, 1652, 1600, 1462 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 1.31 (3 H, s, 12b-CH_3), 1.75 (2 H, m, 1-H and 2-H), 1.89 (1 H, m, 2-H), 2.06 (1 H, m, 1-H), 3.25 (3 H, s, 4-OCH_3), 3.53 (3 H, s, 8-OCH_3 or 11-OCH_3), 3.59 (3 H, s, 11-OCH_3 or 8-OCH_3), 4.41 (1 H, dd, J = 8.0, 8.0 Hz, 3 ax-H), 6.10 (1 H, s, 6-H), 6.22 (1 H, s, 4-H), 6.40 (1 H, d, J = 8.0 Hz, 9-H or 10-H), 6.42 (1 H, d, J = 8.0 Hz, 10-H or 9-H), 8.20 (1 H, s, 7-H), 8.22 (1 H, s, 12-H); $[\alpha]^{21}{}_D$ −176° (c 0.4, benzene); MS m/z 380 (parent, 100), 334 (29). High-resolution mass spectrum: calcd for $C_{23}H_{24}O_5$, 380.162; found: 380.161.

Cis-methoxy diene **15**: colorless amorphous; IR ($CHCl_3$) ν_{max} 3570, 3400 (br), 2930, 1648, 1598, 1461 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 1.29 (3 H, s, 12b-CH_3), 1.71 (1 H, m, 1-H), 1.92 (1 H, m, 2-H), 2.07 (2 H, m, 1-H and 2-H), 3.21 (3 H, s, 4-OCH_3), 3.54 (3 H, s, 8-OCH_3 or 11-OCH_3), 3.59 (3 H, s, 11-OCH_3 or 8-OCH_3), 4.20 (1 H, dd, J = 8.0, 8.0 Hz, 3 ax-H), 5.64 (1 H, s, 4-H), 6.05 (1 H, s, 6-H), 6.42 (1 H, d, J = 8.0 Hz, 9-H or 10-H), 6.43 (1 H, d, J = 8.0 Hz, 10-H or 9-H), 8.22 (1 H, s, 7-H or 12-H), 8.24 (1 H, s, 12-H or 7-H); NOE experiment (benzene-d_6), 5% NOE enhancement of the 3 ax-H signal by the irradiation of 4 ax-H, and 10% NOE of the 4 ax-H signal by the irradiation of 3 ax-H; $[\alpha]^{21}{}_D$ −45° (c 0.1, benzene); MS m/z 380 (parent, 100), 334 (38). High-resolution mass spectrum: calcd for $C_{23}H_{24}O_5$, 380.162; found, 380.162.

Diene-Silyl Ether (−)-12 Derived from Diene-Alcohol (−)-14. To a solution of diene-alcohol **14** (0.010 g) in DMF (1 mL) were added *tert*-butylchlorodimethylsilane (0.009 g) and imidazole (0.007 g) under nitrogen. After being stirred at room temperature for 1.2 h, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water and evaporated in vacuo to dryness. The crude product obtained was purified by a column chromatography on silica gel (hexane/EtOAc 10:1) affording silyl ether (−)-**12** (0.012 g, 92%). All of the spectroscopic data were completely identical with those of the authentic sample of **12** derived from **9**.

Diene-Silyl Ether (+)-13 Derived from Diene-Alcohol (−)-15. Diene-alcohol (−)-**15** (0.035 g) was silylated in the same way as that of (−)-**14** to give silyl ether (+)-**13** (0.044 g, 97%), which was homogeneous with the authentic sample of **13** derived from **9**.

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