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# ABSOLUTE STEREOSTRUCTURES OF HALENAQUINOL AND HALENAQUINOL SULFATE, PENTACYCLIC HYDROQUINONES FROM THE OKINAWAN MARINE SPONGE *XESTOSPONGIA SAPRA*, AS DETERMINED BY THEORETICAL CALCULATION OF CD SPECTRA

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Summary: The absolute stereostructures of two pentacyclic hydroquinones, halenaquinol (1) and halenaquinol sulfate (2) from the Okinawan marine sponge *Xestospongia sapra*, have been determined by means of theoretical calculation of CD spectra.

During the studies on marine natural products,[1] we isolated two yellow pigments named halenaquinol (1) and halenaquinol sulfate (2) from the Okinawan marine sponge *Xestospongia sapra* and elucidated their plane structures.[2] Halenaquinol (1) was readily oxidized either by UV-irradiation or by heating (even at 40°C) in the air to afford halenaquinone (4),[2] an antimicrobial constituent of the Hawaiian marine sponge *Xestospongia exigua*.[3]

Recently, it has begun to be recognized that the π-electron SCF-CI dipole velocity molecular orbital method[4,5] for calculation of CD spectra is a quite useful tool for determination of the absolute stereochemistry of natural products with a distorted π-electron chromophore.[6,7,8] For example, one group of the authors determined the absolute stereochemistry of (+)-1,8a-dihydro-3,8-dimethylazulene by applying the MO method.[6] In this paper, we report the absolute stereostructures of halenaquinol (1) and halenaquinol sulfate (2) as determined by the theoretical calculation of CD spectra.

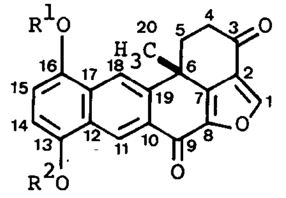
In order to determine the absolute configuration in a reliable manner, several pertinent derivatives (3, 5-10) of halenaquinol (1) were prepared. Methylation of halenaquinol (1) in acetone with $CH_3I-K_2CO_3$ (reflux for 14 h) in the dark furnished the dimethyl ether [(+)-3], yellow needles, $C_{22}H_{18}O_5$,[9] mp 235°C, $[\alpha]_D$ +22°, δ ($CDCl_3$)[10]: 3.98 (6H, s). Treatment of 3 in MeOH-$CH_2Cl_2$ with one molar equivalent of $NaBH_4$ at 20°C in the presence of $CeCl_3 \cdot 7H_2O$[11] selectively afforded the 3β-ol deriv. (5), $C_{22}H_{20}O_5$, δ ($CDCl_3$): 5.00 (1H, dd, J=8.0, 8.0 Hz, 3α-H), which was *tert*-butyldimethylsilylated (TBDMS) to give 6, $C_{28}H_{34}O_5Si$. Further reduction of 6 with $NaBH_4$-$CeCl_3 \cdot 7H_2O$ and subsequent treatment with a catalytic amount of 1N aq. HCl provided two hemiacetals : (-)-8, $C_{29}H_{38}O_5Si$, $[\alpha]_D$ -151°, and (+)-10, $C_{29}H_{38}O_5Si$, $[\alpha]_D$ +20°, in 2:1 ratio.[12] The $^1H$ and $^{13}C$ NMR data for (-)-8[13] indicated presence of the 1α-methoxy-3β-TBDMS-oxy structure in 8, whereas the 1β-methoxy-3β-TBDMS-oxy structure in (+)-10 was substantiated by its $^1H$ and $^{13}C$ NMR spectra[14] and by the NOE enhancement observed between 1α-H and 3α-H (Fig. 1).[15]

Among these derivatives, the naphthalene-diene compounds (-)-8 and (+)-10 are quite suitable for determination of the absolute configuration because their CD spectra are relatively simple in shape, showing intense Cotton effects, as exemplified in Fig. 2. On the other hand, the diketone (+)-3 is unsuitable because of its complex and weak CD Cotton effects. Therefore, we adopted the molecule (11) as a model compound for the calculation of CD spectra (Fig. 3).

The absolute configuration of 11 was arbitrarily chosen to be 6*S* for the calculation. The atomic coordinates were calculated by the method of the molecular mechanics (MMPI).[16] The theoretical calculation of the CD and UV spectra of (6*S*)-11 by the π-electron SCF-CI-DV MO method afforded the curves illustrated in Fig. 3. The UV spectrum curve exhibits two intense $\pi \rightarrow \pi^*$ bands : $\lambda_{max}$ 349 nm (ε 29900) and 219 nm (ε 40300). The calculated values agree closely with the observed UV data for 8: $\lambda_{max}$ 324 nm (ε 27000) and 218 nm (ε 42000).

In the case of CD spectra, these UV transitions yielded three principal Cotton effects: $\lambda_{ext}$ 378 nm (Δε +3.3), 322 nm (Δε -22.4), and 223 nm (Δε +35.5). These calculated values are in good agreement with the observed data for (-)-8: $\lambda_{ext}$ 338 nm (Δε +6.4), 301 nm (Δε -23.3), and 229 nm (Δε +40.9). It is thus evident that the CD spectral data, including the sign and amplitude of the Cotton effects, were well reproduced by the calculation, when Fig. 2 and 3 were compared with each other. The calculated CD curve of (6*S*)-11 also resembles the observed one of (+)-10: $\lambda_{ext}$ 341 nm (Δε +6.1), 302 nm (Δε -15.2), and 231 nm (Δε +29.4). Accordingly, the absolute stereochemistry of the diene derivatives [(-)-8 and (+)-10], halenaquinol (1), and halenaquinol sulfate (2) was theoretically determined to be 6*S*, as shown in structures 8, 10, 1, and 2, respectively.

It should be noted that the absolute configuration of halenaquinol (1) was unambiguously determined by application of the π-electron SCF-CI-DV MO method. The present methodology would become a promising tool for determination of the absolute stereochemistry of various natural products with a distorted π-electron system.

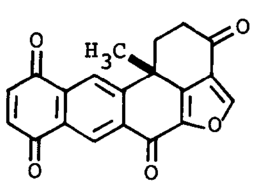


halenaquinol (1): $R^1=R^2=$ H

halenaquinol sulfate (2)

: $R^1=$ $SO_3Na$, $R^2=$ H

3 : $R^1=R^2=$ $CH_3$



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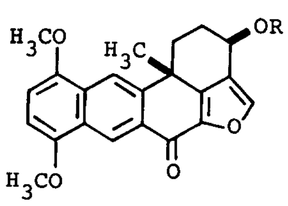
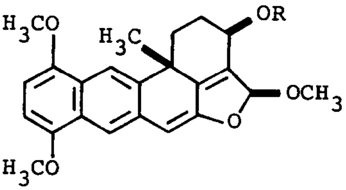
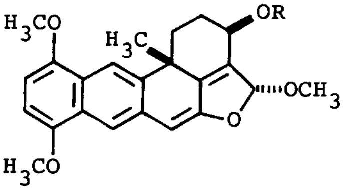


5 : R= H, 6 : R= }-Si+



9 : R= H

10 : R= }-Si+



7 : R= H, 8 : R= }-Si+

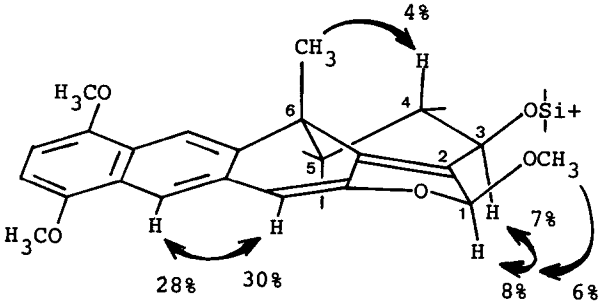


Fig. 1

Fig. 2

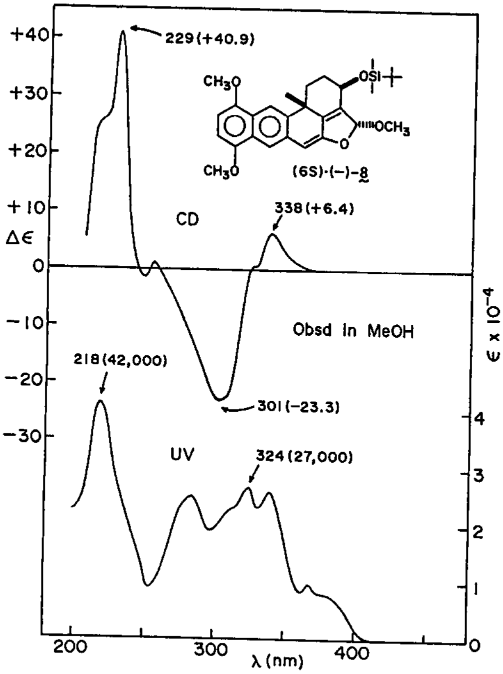
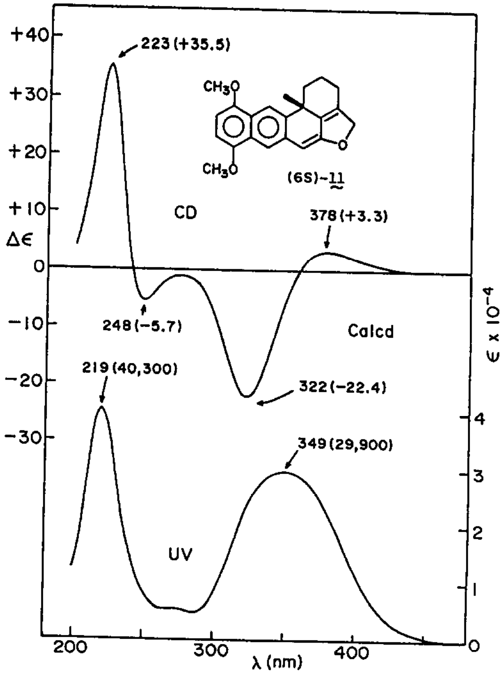


Fig. 3



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## References and Notes

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9) The molecular compositions of compounds with the chemical formulae were determined by high resolution mass spectrometry.
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11) A. L. Gemal and J. L. Luche, J. Am. Chem. Soc., **103**, 5454 (1981).
12) These hemiacetals were also obtained by $NaBH_4$-$CeCl_3$ reduction of **3** followed by HCl treatment, yielding **7**, $C_{23}H_{24}O_5$ [$\delta$ (d$_6$-benzene): 4.41, 1H, dd, J=8.0, 8.0 Hz, 3$\alpha$-H] and **9**, $C_{23}H_{24}O_5$ [$\delta$ (d$_6$-benzene): 4.20, 1H, dd, J=8.0, 8.0, 3$\alpha$-H], and subsequent respective TBDMS derivations.
13) $\delta$ (d$_6$-benzene): 6.22 (1H, s, 1-H), 4.60 (1H, dd, J=8.0, 8.0 Hz, 3$\alpha$-H), 1.9-2.1 (2H, m, 4-H$_2$), 1.85 (1H, ddd, J=13.5, 12.0, 5.0, 5$\alpha$-H), 2.16 (1H, ddd, J=13.5, 3.5, 3.0, 5$\beta$-H), 6.11 (1H, s, 9-H), 8.20 (1H, s, 11-H), 6.41, 6.42 (both 1H, ABq, J=8.0, 14,15-H), 8.25 (1H, s, 18-H), 3.29 (3H, s, 1-OCH$_3$), 1.35 (3H, s, 6-CH$_3$), 3.53, 3.59 (both 3H, s, 13,16-OCH$_3$); $\delta$c (d$_6$-benzene): 99.0 (Dm, C-1), 143.2 (Sm, C-2), 65.6 (Dm, C-3), 34.7 (Tm, C-4), 32.2 (Tm, C-5), 36.9 (Sm, C-6), 140.6 (Sm, C-7), 158.4 (Sd, C-8), 111.4 (Dd, C-9), 133.7 (Sd, C-10), 119.9 (Dd, C-11), 124.9 (St, C-12), 149.9 (2C, St, C-13, 16), 102.9, 103.6 (both Ds, C-14, 15), 126.5 (St, C-17), 117.4 (Ds, C-18), 135.7 (Sm, C-19), 32.5 (Qm, C-20).[17]
14) $\delta$ (d$_6$-benzene): 5.90 (1H, s, 1-H), 4.12 (1H, dd, J=8.0, 8.0 Hz, 3$\alpha$-H), 1.93 (1H, dddd, J=13.0, 8.0, 3.5, 3.0, 4$\alpha$-H), 2.00 (1H, dddd, J=13.0, 12.0, 8.0, 3.0, 4$\beta$-H), 1.82 (1H, ddd, J=13.5, 12.0, 3.0, 5$\alpha$-H), 2.18 (1H, ddd, J=12.5, 3.5, 3.0, 5$\beta$-H), 6.08 (1H, s, 9-H), 8.24 (1H, s, 11-H), 6.42, 6.44 (both 1H, ABq, J=8.0, 14,15-H), 8.29 (1H, s, 18-H), 1.31 (3H, s, 20-H), 3.28 (3H, s, 1-OCH$_3$), 3.55, 3.60 (both 3H, s, 13,16-OCH$_3$), 0.05, 0.09 (both 3H, s), 1.00 (9H, s, TBDMS); $\delta$c (d$_6$-benzene): 97.6 (Dm, C-1), 144.0 (Sm, C-2), 66.7 (Dm, C-3), 34.7 (Tm, C-4), 32.2 (Tm, C-5), 37.0 (Sm, C-6), 140.2 (Sm, C-7), 156.8 (Sd, C-8), 110.2 (Dd, C-9), 133.6 (Sd, C-10), 119.6 (Dd, C-11), 124.8 (St, C-12), 149.8 (2C, St, C-13,16), 102.8, 103.6 (both Ds, C-14,15), 126.4 (St, C-17), 117.4 (Ds, C-18), 134.7 (Sm, C-19), 32.6 (Qm, C-20).
15) In the $^{1}H$ NMR spectrum (d$_6$-benzene) of **9**, irradiation of 1$\alpha$-H resulted in 5% NOE enhancement of the 3$\alpha$-H signal ($\delta$ 4.20, 1H, dd, J=8.0, 8.0 Hz) and 10% NOE for 1$\alpha$-H signal ($\delta$ 5.64, 1H, s) upon irradiation of 3$\alpha$-H.
16) N. L. Allinger, QCPE, **11**, 318 (1976); QCPE Program #318.
17) Abbreviations given in the parentheses denote the signal patterns (capital letters refer to the pattern arising from directly bonded protons, and lower-case letters to long-range $^{13}C$-$^{1}H$ couplings: S or s=singlet, D or d=doublet, T or t=triplet, Q or q=quartet, m=multiplet).

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