The Absolute Configuration of Avarol, a Rearranged Sesquiterpenoid Hydroquinone from a Marine Sponge

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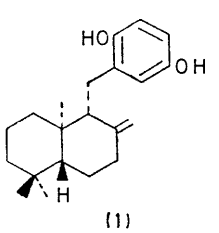
With the aid of circular dichroism, n.m.r. shift reagents, and ^{13}C n.m.r. spectroscopy the absolute stereochemistry has been assigned to avarol {2-[(1*R*)-1,2,3,4,4a,7,8,8aα-octahydro-1β,2β,4aβ,5-tetramethyl-1-naphthylmethyl]-hydroquinone}, obtained from the marine sponge *Disidea avara*. Avarol is the first naturally occurring sesquiterpenoid of the 9,4-friedodrimane type to be isolated.

MARINE organisms, particularly algae and sponges, have recently yielded a series of compounds having a terpenoid skeleton linked to a hydroquinone or quinone residue. The brown seaweed *Dictyopteris undulata* (= *zonarioides*) has yielded a sesquiterpene-substituted hydroquinone zonarol (1),[1] accompanied by minor amounts of the derived chromazonarol (2),[2] with the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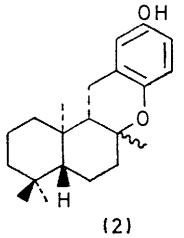
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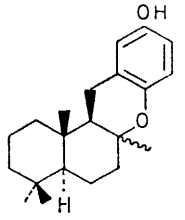
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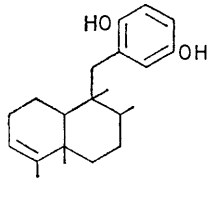
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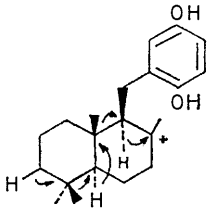
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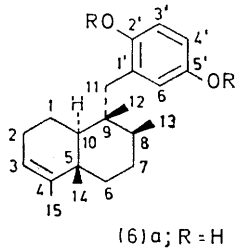
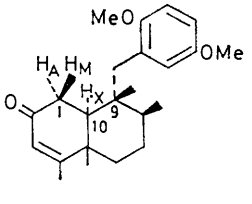

(6) a; R = H
b; R = Me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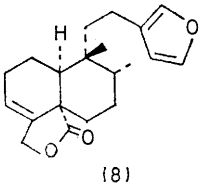
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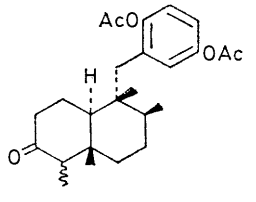

(9)

absolute configurations illustrated.[3] The enantiomeric chromazonarol (3) has been reported to occur in the sponge *Disidea pallescens*.[4] We have recently described the gross structure of a further sesquiterpene-substituted hydroquinone, avarol (4), from the related sponge *D. avara*.[5] This structure (4) represents the first 9,4-friedodrimane type in sesquiterpenoids and may arise by a biogenetic pathway involving rearrangements of the ion (5), on the assumption that avarol and *ent*-chromazonarol (3) are genetically related. We now show that the absolute configuration of avarol is as shown in (6a), thus supporting the initial postulate that avarol and *ent*-chromazonarol are biogenetically related.

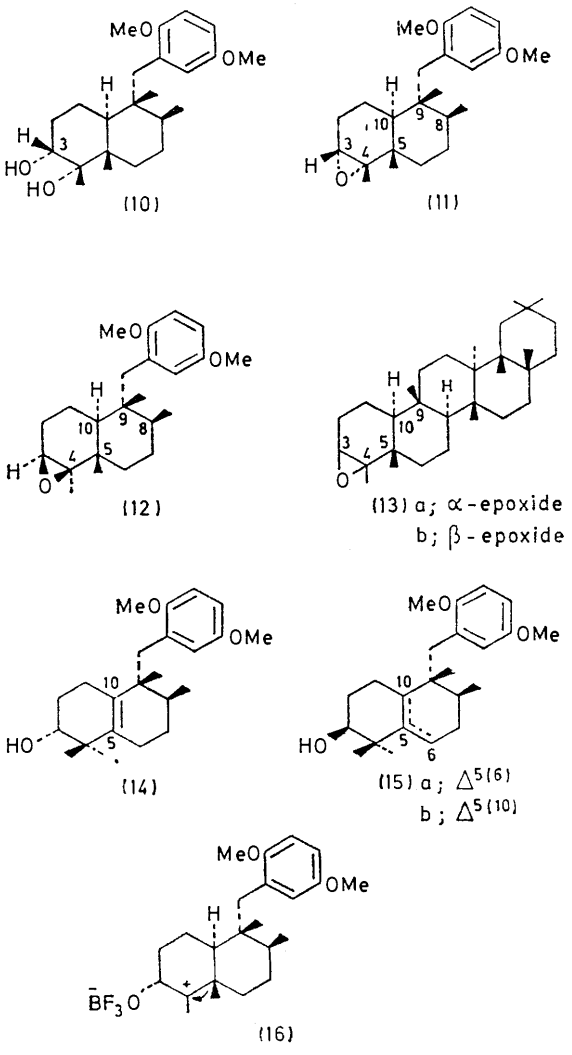
Oxidation of avarol dimethyl ether (6b) with chromium trioxide–pyridine complex slowly produced the enone (7), in the n.m.r. spectrum of which (solvent C_6D_6) the signals for H-10 and the two C-1 protons formed a clean isolated AMX system with line positions at δ 3.20, 2.30, and 1.80 for H-1*eq* (A), H-1*ax* (M), and H-10 (X), respectively. Analysis of this system by double irradiation experiments gave values for J_{AX} (3 Hz) and J_{MX} (13.5 Hz). The magnitudes of these coupling constants revealed that H-10 (X) is axial to ring A and accordingly that the compound has either a

[1] W. Fenical, J. J. Sims, R. M. Wing, and P. Radlik, *J. Org. Chem.*, 1973, **38**, 2383.
[2] W. Fenical and O. McConnell, *Experientia*, 1975, **31**, 1004.
[3] G. Cimino, S. De Stefano, W. Fenical, L. Minale, and J. J. Sims, *Experientia*, 1975, **31**, 1250.
[4] G. Cimino, S. De Stefano, and L. Minale, *Experientia*, 1975, **31**, 1117.
[5] L. Minale, R. Riccio, and G. Sodano, *Tetrahedron Letters*, 1974, 3401.

trans-AB ring fusion or a *cis*-fusion in the conformation with H-10 axial. The enones corresponding to (7) derived from diterpenoids based on a *cis*-clerodane skeleton are known to prefer a ' steroid-like ' conformation with H-10 equatorial,[6-8] unless a constraint imposes a non-steroidal conformation such as in the lactone (8) derived from the naturally occurring solidagoic acid B.[9] On this basis the *trans*-AB ring fusion for avarol seems favoured. The enone (7) showed a strong positive c.d. Cotton effect for $n \longrightarrow \pi^*$ transition ($[\theta]_{320}$ +6 075). Since the deduction of absolute configuration from the Cotton effects of αβ-unsaturated ketones is known to be fraught with difficulties, c.d. measurements were also performed on the ketone (9), prepared by hydroboration–oxidation of avarol diacetate. On the assumption of a *trans*-ring junction the strong negative Cotton effect exhibited by the ketone (9) ($[\theta]_{187}$ −7 866) leads to the assignment of the 5β,10α-absolute configuration as indicated and, on the basis of Snatzke's rules [10] for *transoid* enones, the positive Cotton effect exhibited by (7) could also be in accord with this.

During work on the constitution of avarol, osmylation of the dimethyl ether (6b) gave, in quantitative yield, a single diastereoisomer of the α-glycol (10), in the n.m.r. spectrum of which the H-3 signal appeared as a double doublet with splittings of 5 and 10 Hz (axial H). On the assumption of a *trans*-AB ring fusion, a 3α,4α-glycol might be expected from the osmylation reaction since the β-face appears more hindered. This was substantiated by determining the chirality of the glycol system of (10) by the simple method of Nakanishi and Dillon,[11] which employs the induced Cotton effect observed in the c.d. spectra of a mixture of the α-glycol and the shift reagent Eu(dpm)$_3$ or Pr(dpm)$_3$ in carbon tetrachloride. A *ca.* 1 : 1 mixture of (10) and Eu(dpm)$_3$ in carbon tetrachloride gave, as expected, a positive Cotton effect at the longer wavelength (*ca.* 305 nm), indicating a positive chirality (clockwise rotation from one hydroxy-group to the other) for the glycol system.

Even though a *trans*-AB ring fusion for avarol is strongly favoured, a *cis*-fusion cannot be rigorously excluded by the foregoing evidence. This question was solved by application of the shift reagent Eu([$^2H_9$]fod)$_3$ [12,13] to a study of the diastereoisomeric epoxides (11) and (12) obtained by treatment of avarol dimethyl ether (6b) with *m*-chloroperbenzoic acid; the results also gave an indication of the stereochemistry at C-9. The stereochemistry at C-3 and C-4 in the epoxides was easily deduced from the multiplicity of the H-3 resonance. In the more polar isomer (11), $[\alpha]_D$ +27.0°, the H-3 signal appears as a double doublet (*J* 2 and 3.5 Hz) and in the less polar (12), $[\alpha]_D$ +5.8°, as a singlet ($W_{\frac{1}{2}}$ 3 Hz). The shifts induced by Eu([$^2H_9$]fod)$_3$ are given in Table 1. Aromatic ethers are virtually inert



towards Eu(fod)$_3$; hence the two epoxides are essentially monofunctional. For the purpose of comparison it was convenient to normalize the induced paramagnetic shifts to give a value of 10.0 to Δ[δ(Eu) − δ($CDCl_3$)] for the lowest field methyl signal. Comparison of the relative magnitudes of the induced shifts of the 4- and 5-methyl signals revealed the relative stereochemistry between the oxiran ring and the angular methyl group: in (11), the epoxide must be situated *anti*, and in (12) it must be situated *syn*, as in the former the 4-methyl and in the latter the 5-methyl signal shows the largest paramagnetic shift, respectively. In the more polar isomer

[6] G. Berti, O. Livi, and D. Segnini, *Tetrahedron Letters*, 1970, 1401.
[7] T. J. King and S. Rodrigo, *Chem. Comm.*, 1967, 575; T. J. King, S. Rodrigo, and S. C. Wallwork, *ibid.*, 1969, 683.
[8] A. B. Anderson, R. McCrindle, and E. Nakamura, *J.C.S. Chem. Comm.*, 1974, 453; G. Ferguson, W. C. Marsh, R. McCrindle, and E. Nakamura, *ibid.*, 1975, 299.
[9] T. Anthonsen, M. S. Henderson, A. Martin, R. D. H. Murray, R. McCrindle, and D. McMaster, *Canad. J. Chem.*, 1973, **51**, 1332.
[10] G. Snatzke, in ' Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry,' ed. G. Snatzke, Heyden, London, 1967, p. 208.
[11] K. Nakanishi and J. Dillon, *J. Amer. Chem. Soc.*, 1971, **93**, 4058; see also N. Harada and K. Nakanishi, *Accounts Chem. Res.*, 1972, **5**, 257.
[12] A. F. Cockerill, G. L. O. Davies, R. C. Harden, and D. M. Rackham, *Chem. Rev.*, 1973, **73**, 553.
[13] B. C. Mayo, *Chem. Soc. Rev.*, 1973, **2**, 49.

(11), the H-10 signal is more strongly shifted to lower field than the epoxide proton; this is consistent only with its *syn*-relationship to the epoxide ring and accordingly a *trans*-AB ring fusion is required. The similarity between the induced shifts in the pairs avarol dimethyl ether α-epoxide–friedelane 3α,4α-epoxide (13a) and avarol dimethyl ether β-epoxide–friedelane 3β,4β-epoxide (13b) (see Experimental section) confirms this view.

TABLE 1

' Normalized ' Eu([$^2H_9$]fod)$_3$-induced shifts [a] of compounds (11), (12), (17), and (18)

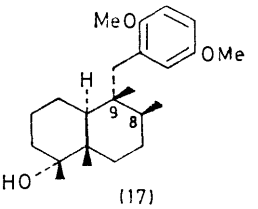
	4-CH_3	5-CH_3	9-CH_3	8-CH_3	9-CH_2	3-H	10-H
(11)	10	7.3	5.4	2.8	6.4	16.1	33.9 [b]
(12)	8.6	10	2.9	1.9	2.6	20.6	*c*
(17)	10	4.8	3.7	1.9	4.7		
(18)	10	9.7	2.7	1.8	2.2	25.3	

[a] $\Delta[\delta(Eu) - \delta(CDCl_3)]$ Values relative to the lowest field methyl signal ($\Delta = 10$) and ' normalized ' for 1 : 1 mol ratio {Eu([$^2H_9$]fod)$_3$ to substrate}; 0.02M-solutions in $CDCl_3$. [b] Assignment is based on the shape of the signal and decoupling experiments: the H-10 signal appears as a dd with J 12.5 and 3 Hz(axial H) in the spectrum of (11) after the addition of Eu([$^2H_9$]fod)$_3$; irradiation at the H-3 frequency left its shape unchanged. This ruled out the possibility of the signal being due to H-2, and H-1*ax* is excluded because this proton is expected to be *anti* to the oxiran ring. [c] At both low and increased concentration of Eu([$^2H_9$]fod)$_3$ no peaks were visible for H-10, being overlapped with other methylene and methine signals.

These stereochemical conclusions also explain the difference in reactivity of the epoxides (11) and (12) towards boron trifluoride–ether complex. The epoxide (11) furnished exclusively the rearranged hydroxy-olefin (14), whereas (12) gave the $\Delta^{5(6)}$ (15a) and $\Delta^{5(10)}$ (15b) olefins in approximately equal amounts. *trans*-Clerodane diterpenoid 3,4-epoxides are reported to behave similarly on exposure to boron trifluoride–ether, and McCrindle and Nakamura [14] have offered a plausible explanation: in the case of the α-epoxide (11), as the epoxide ring opens, the C-3 oxygen function is suitably disposed to remove the C-10 proton [in (16) or related species] in an intramolecular process, forming the tetrasubstituted olefin; in the case of the β-epoxide (12) either the C-10 or the C-6α proton, both of which are *trans*-antiparallel to the C-5 methyl group, is removed in an intermolecular reaction.

Further, the stereochemistry assigned to C-9 is required to explain the relative magnitudes of the induced shifts of the n.m.r. signals of the attached methyl and methylene groups in (11) and (12): in (11) the epoxide ring must be nearer the methylene group and in (12) it must be nearer the methyl group, as in the former the C-9 methylene protons and in the latter the C-9 methyl protons show the larger paramagnetic shifts.

In order to confirm the stereochemistry at C-9 and to ascertain the stereochemistry at the remaining chiral centre, C-8, we applied the n.m.r. shift reagent to the alcohols (17) and (18) obtained by ring opening of the epoxides (11) and (12), respectively, with lithium aluminium hydride. The stereochemistry of the cyclohexene oxide cleavage with nucleophilic reagents (*trans* and diaxial) is well established [15] and, as expected, both the α- and the β-epoxide produced exclusively the corresponding axial alcohol. The results of the shift reagent studies (Table 1) reinforced the previous conclusions. The 3β-alcohol (18) produced patterns for the 4-, 5-, and 9-methyl groups very similar to those observed for friedelan-3β-ol, whose spectrum in the presence of Eu(dpm)$_3$ has been reported recently.[16] The shifts observed for the C-8 methyl group in (17) and (18) are such that it does not seem feasible to determine whether this group is α- or β-oriented. However even though the β-equatorial stereochemistry at C-8 of avarol can be tentatively advanced on a biogenetic basis, we decided to investigate the question further with the aid of ^{13}C n.m.r. spectroscopy, which we expected would provide confirmatory evidence for the stereochemistry of all centres.



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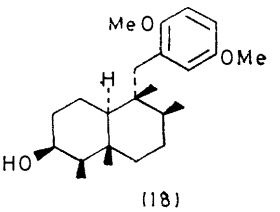

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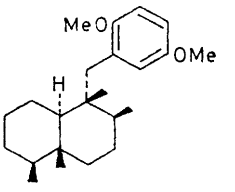

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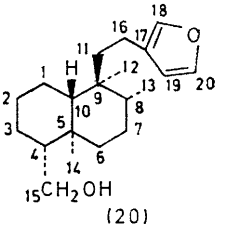

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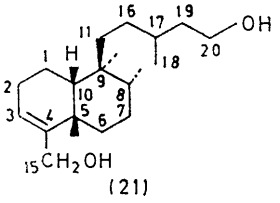

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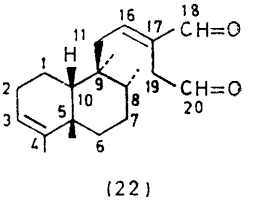

(22)

The ^{13}C n.m.r. spectra of avarol dimethyl ether (6b) and its dihydro-derivative (19) (obtained as a single 4β-equatorial methyl epimer by hydrogenation over Pd–C because of addition of hydrogen from the less hindered α-side of the molecule) were compared with that of the model compound (20) and also with those of some *cis*-clerodane diterpenoids, such as cistodiol (21) [6] and linaradial (22).[17] The *trans*-clerodane diterpenoid

[14] R. McCrindle and E. Nakamura, *Canad. J. Chem.*, 1974, **52**, 2029.

[15] M. N. Rerick, in ' Reduction,' ed. R. L. Augustine, Dekker, New York, 1968, p. 53.

[16] R. B. Lewis and E. Wenkert, in ' Nuclear Magnetic Resonance Shift Reagents,' ed. R. E. Sievers, Academic Press, New York and London, 1973, p. 99.

[17] I. Kitagawa, M. Yoshihara, T. Tani, and I. Yosioka, *Tetrahedron Letters*, 1975, 23.

(20) is reported [18] to be obtained by reduction with lithium aluminium hydride of the corresponding naturally occurring carboxylic acid, whose stereochemistry was established by inter-relation with (—)-hardwickiic acid.[19]

TABLE 2

^{13}C N.m.r. chemical shifts * for avarol dimethyl ether (6b), its dihydro-derivative (19), and the *trans*-clerodane diterpenoid (20)

	(6b)	(19)	(20)
C-1	19.5	22.3	21.6
C-2	26.4 [a]	26.4 [a]	27.3 [a]
C-3	120.5	30.4	25.5
C-4	144.5	45.1	54.5
C-5	41.8	41.3	37.0
C-6	37.0 [b]	38.0	38.6 [b]
C-7	27.6 [a]	27.1 [a]	27.0 [a]
C-8	36.0	36.7 [b]	36.5
C-9	38.2	38.7	38.8
C-10	45.8	48.9	49.8
C-11	35.7 [b]	35.8 [b]	39.5 [b]
C-12	17.1	16.9	16.1
C-13	17.5	17.1	18.2
C-14	17.8	14.4	15.2
C-15	19.8	12.6	63.6
C-16			29.8
C-17			126.0
C-18			142.9
C-19			111.2
C-20			138.7
C-1′	129.1	129.4	
C-2′	153.3	153.4	
C-3′	111.1	111.4	
C-4′	111.0	111.0	
C-5′	153.1	153.6	
C-6′	119.4	119.2	
OMe	55.4	55.3	
OMe	55.3	55.1	

* Spectra were determined at 25.20 MHz with a Varian XL-100 Fourier transform spectrometer, operating in both proton-noise decoupled and off-resonance decoupled modes. Chemical shifts are given in p.p.m. with respect to internal Me_4Si.

[a,b] Assignments may be reversed, although those given here are preferred.

The models with a *cis*-AB ring junction produced ^{13}C n.m.r. spectra clearly distinct from those produced by the *trans*-compounds and the basic differences were, as expected, the chemical shifts of the angular methyl carbon atoms. Stothers' group has recently shown that AB-*cis*- and -*trans*-steroidal systems can be differentiated by the C-19 signals: that of the *trans*-isomer occurs *ca.* 11—12 p.p.m. upfield from that of the *cis*-isomer,[20] and the same differences have been observed in *cis*- and *trans*-9-methyldecalin, in which the methyl shieldings differ by 12.4 p.p.m.[20,21] In the off-resonance-decoupled spectra of compounds (21) and (22), quartets from the methyl carbon atoms are visible at 16.0, 17.5, 19.9, and 35.1 and at 16.2, 16.4, 19.5, and 32.5 p.p.m., respectively; whereas the chemical shifts of the methyl carbons in the *trans*-compounds lie in the range 12.6—19.8 p.p.m. (see Table 2). We assume that the low-field methyl signals in the *cis*-models correspond to the angular methyl groups. Thus the C-5 methyl shieldings clearly reflect the stereochemistry of the AB ring junction in 9,4-friedo-sesqui- and -di-terpenoids, and the differences are so large that one can determine the AB ring geometry from the spectrum of an individual isomer. The 3.0 p.p.m. shift to lower field of the C-5 methyl carbon signal on going from (22) to (21) could be explained by the deshielding δ-interaction in (21) between the hydroxy-group on C-15 and the C-5 methyl group.[22,23] The assignments of the carbon signals of avarol dimethyl ether (6b), its dihydro-derivative (19) and the model compound (20) are reported in Table 2. Comparison of the spectra of (6b) and (19) allowed us to distinguish between the methine carbon signals and to assign the resonance of the C-1 methylene carbon atom on the assumption that the incorporation of the double bond in ring A of (6b) would result in shielding of the homoallylic carbon atoms.[24] This endocyclic homoallylic effect is actually exhibited by C-10 (3.1 p.p.m.) and C-1 (2.8 p.p.m.) in (6b). The doublet at 45.1 p.p.m. in the spectrum of (19) can be easily assigned to C-4, as in the spectrum of (20) the signal occurs 9.4 p.p.m. downfield as a result of the deshielding β-effect [22] due to the hydroxy-group at C-15. This leaves the doublet in the range 36.0—36.7 to C-8. In agreement with the effect of replacement of a hydrogen atom with a hydroxy-group, the γ-carbon atoms [22] C-3 and C-5 of (20) resonates *ca.* 5 p.p.m. to higher field than C-3 and C-5 in (19). This leaves the off-resonance singlet in the 38.2—38.8 p.p.m. range to the remaining quaternary sp^3 site (C-9). Among the remaining methylene resonances, the two at higher field (26.4—27.6 p.p.m.) whose shifts are nearly invariant in the spectra of all three compounds, are assigned to C-2 and C-7 (their differentiation appears difficult; assignments are based on methyl substituent parameter calculation [21]). The methylene resonances at 37.0 and 35.7 for (6b) and at 38.0 and 35.8 p.p.m. for (19) can then be assigned to C-6 and C-11 or *vice versa*; the same carbon atoms in (20) resonate at 38.8 and 39.5 p.p.m. or *vice versa*, and the remaining methylene signal at 29.8 p.p.m. in the spectrum of the latter is due to C-16 [it is absent in the spectra of (6b) and (19)]. Although the differentiation of C-6 and C-11 is difficult in the spectra of all three compounds, the downfield shift found for C-6 in (20) relative to (6b) and (19) is the expected consequence of the deshielding δ-effect of the hydroxy-group. A similar δ-effect could also account for the downfield shift found for C-10 in (20) relative to (19), and the preferred assignments given in Table 2 for C-2 and C-7 are also based on the δ-interaction between

[18] M. Ferrari, F. Pellizzoni, and G. Ferrari, *Phytochemistry*, 1971, **10**, 3267.
[19] R. Misra, R. C. Panday, and Sukh Dev, *Tetrahedron Letters*, 1964, 3751; 1968, 2681.
[20] J. L. Gough, J. P. Guthrie, and J. B. Stothers, *J.C.S. Chem. Comm.*, 1972, 979.
[21] D. K. Dalling, D. M. Grant, and E. G. Paul, *J. Amer. Chem. Soc.*, 1973, **95**, 3718.
[22] J. B. Stothers, 'Carbon-13 NMR Spectroscopy,' Academic Press, New York, 1972.
[23] S. H. Grover and J. B. Stothers, *Canad. J. Chem.*, 1974, **52**, 870; S. H. Grover, J. P. Guthrie, J. B. Stothers, and C. T. Tan, *J. Magnetic Resonance*, 1973, **10**, 227.
[24] E. Wenkert, D. W. Cochram, E. W. Hagaman, F. M. Schell, N. Neuss, A. S. Katner, P. Poitier, C. Kan, M. Plat, M. Koch, H. Meheri, J. Poisson, N. Kunesh, and Y. Rolland, *J. Amer. Chem. Soc.*, 1973, **95**, 4990.

the hydroxy-group and C-2 in (20). The assignment of the signals of the aromatic carbon atoms in (6b) and (19) and to the furan carbon atoms in (20) is based on consideration of chemical shift rules.[22] The methyl resonances were not assigned.

The stereochemistry of avarol as shown in (6) is well supported by this ^{13}C n.m.r. study. Particularly diagnostic for the equatorial orientation of the methyl group at C-8 are the chemical shifts of C-6, C-8, and C-10.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. Column chromatography was carried out on silica gel (0.05—0.2 mm; Merck). T.l.c. was carried out on silica gel (Merck 60 F_{254}) and spots were located by spraying with cerium sulphate in sulphuric acid (100 mg in 10 ml). I.r. spectra were measured for solutions in chloroform with a Perkin-Elmer 257 Infracord, u.v. spectra for solutions in methanol with a Bausch and Lomb Spectronic, and ^1H n.m.r. spectra for solutions in [^2H]chloroform with a Varian HA-100 spectrometer (tetramethylsilane as internal reference) unless otherwise indicated. Mass spectra were measured with an A.E.I. MS30 instrument at 70 eV; accurate mass measurements were performed with an A.E.I. MS902 instrument. C.d. curves were recorded with a FICA Spectropolarimeter. Rotations were measured for solutions in chloroform.

Avarol Dimethyl Ether (6b).—Avarol (6a) (1 g) in ethanol (5 ml) was treated with dimethyl sulphate (1.5 ml) and aqueous 25% w/v sodium hydroxide (4 ml) (both added in portions) at reflux for 3 h. Work-up as usual and purification by column chromatography [benzene–light petroleum (b.p. 40—70°), 7 : 3] followed by crystallization from ethanol afforded the *dimethyl ether* (6b) (810 mg) as rods, m.p. 80—81° (Found: C, 80.1; H, 9.8. $C_{23}H_{34}O_3$ requires C, 80.65; H, 10.0%), $[\alpha]_D$ +5.2 (*c* 1.7), δ 0.86 and 1.03 (each 3 H, s, tert. CH_3), 1.01 (3 H, d, *J* 6 Hz, partially overlapped with 1.03 singlet, 8-CH_3), 1.52 (3 H, d, *J* 1 Hz, 4-CH_3), 2.68 (2 H, s, 9-CH_2), 3.72 and 3.74 (6 H, each s, OCH_3), 5.13 (1 H, m, H-3), and 6.72br (3 H, s, aromatic); *m/e* 342 (M^+, 0.3%), 206 (3), 191 (5), 152 (48), 151 (23), 121 (32), and 95 (100).

Oxidation of the Dimethyl Ether (6b) *by Chromium Trioxide–Pyridine*.—The dimethyl ether (6b) (100 mg) in pyridine (5 ml) was added to chromium trioxide (110 mg) in pyridine (2 ml); the mixture was stirred at room temperature for 30 days, treated with ethanol (1.5 ml) for 15 min, and then diluted with water (25 ml). Extraction with ether, followed by preparative t.l.c. [benzene–light petroleum (b.p. 40—70°) (8 : 2 v/v)] afforded, in addition to unchanged (6b) (48 mg), the oily *enone* (7) (25 mg) (Found: M^+, 356.2361. $C_{23}H_{32}O_3$ requires *M*, 356.2351), $[\alpha]_D$ −100.8° (*c* 0.6); $\nu_{max.}$ (film) 1 655 cm^{-1}; $\lambda_{max.}$ 229, 245sh, and 293 nm (log ε 4.21, 4.05, and 3.65); δ 0.92 and 1.14 (3 H each, s, tert. CH_3), 1.03 (3 H, d, *J* 6 Hz, 8-CH_3), 1.77 (3 H, d, *J* 1 Hz, 4-CH_3), 2.39 (1 H, dd, *J* 17 and 13 Hz, H-1*ax*), 2.44 and 2.87 (2 H, ABq, *J* 13 Hz, 9-CH_2), 3.04 (1 H, dd, *J* 17 and 3 Hz, H-1*eq*), 3.66 and 3.70 (each 3 H, s, OCH_3), 5.62br (1 H, s, H-3), and 6.65br (3 H, aromatic), δ(C_6D_6) 0.70 and 0.80 (each 3 H, s, tert. CH_3), 0.97 (3 H, d, *J* 6 Hz, 8-CH_3), 1.27 (3 H, d, *J* 1 Hz, 4-CH_3), 1.80 (1 H, dd, *J* 13 and 3 Hz, H-10), 2.30 (1 H, dd, *J* 16 and 13 Hz, H-1*ax*), 2.44 and 2.87 (each 1 H, d, *J* 14 Hz, 9-CH_2), 3.20br (1 H, dd, *J* 16 and 3 Hz, H-1*eq*), 3.49 and 3.51 (6 H, each s, OCH_3), 5.70br (1 H, s, H-3), 6.45 (1 H, d, *J* 9 Hz, H-3′), 6.63 (1 H, dd, *J* 9 and 3 Hz, H-4′), and 6.86 (1 H, d, *J* 3 Hz, H-6′); c.d. (ethanol) $[\theta]_{320}$ +6 075, $[\theta]_{256}$ −15 800; *m/e* 356 (M^+, 11%), 205 (0.4), 152 (100), and 151 (2).

Hydroboration–Oxidation of Avarol Diacetate.—The *diacetate* [prepared with an excess of acetic anhydride in pyridine at room temperature (3 h)] crystallized from ethanol–water; m.p. 92—93° (Found: C, 75.0; H, 8.4. $C_{25}H_{34}O_4$ requires C, 75.3; H, 8.6%); $\nu_{max.}$ ($CHCl_3$) 1 760 and 1 205 cm^{-1}; δ 2.24 and 2.06 (OAc); *m/e* 398 (M^+, 23%), 191 (100), 175 (27), 121 (28), 107 (55), and 95 (98).

To a solution of the diacetate (120 mg) in dry ether (3 ml), sodium borohydride (60 mg) and zinc chloride (15 mg) were added, followed slowly by a solution of boron trifluoride–ether (0.6 ml) in dry ether (3 ml), and the resulting mixture was stirred at room temperature for 2 h. An excess of Jones reagent was added, and the mixture was refluxed for 2 h and then diluted with water. The product was extracted with ether and the combined extracts were washed with water, aqueous sodium hydrogen carbonate, and water again, dried ($MgSO_4$), and evaporated. Crystallization from ethanol gave the *ketone* (9) (80 mg), m.p. 207—213° (Found: C, 72.9; H, 8.5. $C_{25}H_{34}O_5$ requires C, 72.4; H, 8.3%); $\nu_{max.}$ 1 760 and 1 706 cm^{-1}; δ 0.75 and 0.87 (3 H each, s, tert. CH_3), 0.82 (3 H, d, *J* 7 Hz, 4-CH_3; collapses to s on irradiation at δ 2.2), 1.00 (3 H, d, *J* 6 Hz, 8-CH_3), 2.25 and 2.28 (3 H each, s, OAc), and 2.57 (2 H, s, 9-CH_2); *m/e* 414 (M^+, 0.2%), 207 (100), 189 (40), 166 (73), 124 (40), 123 (40), 109 (23), and 95 (26); c.d. (methanol) $[\theta]_{287}$ −7 866.

Oxidation of the Dimethyl Ether (6b) *with Osmium Tetraoxide*.—A mixture of (6b) (102 mg, 0.3 mmol) and osmium tetraoxide (76.2 mg, 0.3 mmol) in dry pyridine (1 ml) was stirred at room temperature for 3 h. Aqueous sodium hydrogen sulphite (55 mg in 5 ml) and pyridine (1 ml) were added, and the mixture was stirred for 1 h. Extraction with methylene chloride and evaporation to dryness gave the *glycol* (10), which crystallized from n-heptane; yield 100 mg; m.p. 138—140° (Found: C, 72.9; H, 9.4. $C_{23}H_{36}O_4$ requires C, 73.4; H, 9.6%); $[\alpha]_D$ −15.7 (*c* 2); $\nu_{max.}$ ($CHCl_3$) 3 600—3 300 cm^{-1}; δ 0.84 and 0.95 (each 3 H, s, tert. CH_3), 0.97 (3 H, d, *J* 6 Hz, 8-CH_3), 1.10 (3 H, s, 4-CH_3), 2.55 and 2.77 (2 H, ABq, *J* 14 Hz, 9-CH_2), 3.58 (1 H, dd, *J* 10 and 5 Hz, H-3), 3.66 and 3.88 (each 3 H, s, OCH_3), and 6.76 (3 H, m, aromatic); *m/e* 376 (M^+, 4%), 358 (1), 356 (1), 207 (16), 189 (14), and 152 (100); c.d. [solution of (10) and $Eu(dpm)_3$ in dry carbon tetrachloride; both solutes 2.8×10^{-4}M] $[\theta]_{305}$ +10 600 (spectrum measured after 30 min).

Epoxidation of Avarol Dimethyl Ether (6b).—The dimethyl ether (6b) (230 mg) was treated with *m*-chloroperbenzoic acid (250 mg) in chloroform (25 ml) at room temperature for 6 h. The resulting solution was washed with aqueous sodium carbonate (5%; twice) and water and evaporated *in vacuo*. Column chromatography in 8 : 2 benzene–light petroleum (b.p. 40—70°) furnished the less polar oily β-*epoxide* (12) (70 mg), $[\alpha]_D$ +5.8° (*c* 2) (Found: M^+, 358.2512. $C_{23}H_{34}O_3$ requires *M*, 358.2508), $\nu_{max.}$ (film) 1 500, 1 445, 1 220, and 1 050 cm^{-1}; δ 0.78 (3 H, s, 9-CH_3), 0.98 (3 H, d, *J* 5 Hz, 8-CH_3), 1.08 (3 H, s, 5-CH_3), 1.11 (3 H, s, 4-CH_3), 2.62 (2 H, s, 9-CH_2), 2.83br (1 H, s, $W_{\frac{1}{2}}$ 3 Hz, H-3), and 3.72 and 3.77 (6 H, each s, OCH_3); with 0.6 : 1 molar ratio of Eu([$^2H_9$]fod)$_3$ to (12), δ 1.66 (3 H, d, *J* 5 Hz, 8-CH_3), 1.78 (3 H, s, 9-CH_3), 3.42 and 3.74 (each 1 H, d,

J 16 Hz, 9-CH_2), 4.14 and 4.18 (6 H, each s, OCH_3), 4.75 (3 H, s, 4-CH_3), 5.26 (3 H, s, 5-CH_3), and 10.20br (1 H, s, H-3); *m/e* 358 (M^+, 8%), 342 (1), 207 (10), 189 (14), and 152 (100). The more polar α-*epoxide* (11) (102 mg) had $[\alpha]_D$ +27.04° (*c* 2) (Found: M^+, 358.2502); $\nu_{max.}$ (film) 1 495, 1 455, 1 220, and 1 050 cm^{-1}; δ 0.80 (3 H, s, 9-CH_3), 0.94 (3 H, d, *J* 5.5 Hz, 8-CH_3), 1.06 (3 H, s, 5-CH_3), 1.12 (3 H, s, 4-CH_3), 2.57 (2 H, s, 9-CH_2), 2.80 (1 H, dd, *J* 2 and 3.5 Hz, H-3), and 3.70 and 3.76 (6 H, each s, OCH_3); with 0.64 : 1 molar ratio of Eu([$^2H_9$]fod)$_3$ to (11), δ 1.34 (3 H, d, *J* 5.5 Hz, 8-CH_3), 1.58 (3 H, s, 9-CH_3), 2.12 (3 H, s, 5-CH_3), 2.58 (3 H, s, 4-CH_3), 3.35 and 3.65 (2 H, ABq, *J* 14 Hz, 9-CH_2), 3.78 (3 H, s, OCH_3), 3.98 (3 H, s, OCH_3), 5.18 (1 H, d, *J* 4 Hz, H-3), and 6.48br (1 H, d, *J* 12 Hz, H-10); *m/e* 358 (M^+, 4.5%), 342 (1), 207 (14), 189 (20), and 152 (100).

Reduction of the α-*Epoxide* (11) *with Lithium Aluminium Hydride*.—The epoxide (11) (25 mg) was stirred with an excess of lithium aluminium hydride in dry ether for 6 h. Work-up with water and aqueous N-hydrochloric acid afforded the *alcohol* (17) (24 mg), m.p. 90° [from light petroleum (b.p. 40—70°)] (Found: M^+, 360.2660. $C_{23}H_{36}O_3$ requires *M*, 360.2664); δ 0.89 (3 H, s, 9-CH_3), 1.03 (s) and 1.05 (s) overlapped with a doublet (*J* 6 Hz) centred at 1.04 (9 H, 5-, 4-, and 8-CH_3), 2.68 (2 H, s, 9-CH_2), 3.72 and 3.75 (6 H, each s, OCH_3), and 6.72br (3 H, s, aromatic); with 0.65 : 1 molar ratio of Eu([$^2H_9$]fod)$_3$ to (17), δ 1.33 (3 H, d, *J* 6 Hz, 8-CH_3), 1.55 (3 H, s, 9-CH_3), 1.95 (3 H, s, 5-CH_3), 2.81 (3 H, s, 4-CH_3), 3.36 and 3.56 (2 H, ABq, *J* 13 Hz, 9-CH_2), 3.98 and 4.16 (each 3 H, s, OCH_3), 4.50br (1 H, m, H-2*ax*), and 5.54br (1 H, d, *J* 11 Hz, H-10); *m/e* 360 (M^+, 3), 191 (56), and 152 (100).

Reduction of the β-*Epoxide* (12) *with Lithium Aluminium Hydride*.—The epoxide (12) (20 mg), when treated with excess of lithium aluminium hydride as before, afforded the oily *alcohol* (18) (16 mg) (Found: M^+, 360.2671); δ 0.83 (3 H, s, 9-CH_3), 0.86 (3 H, d, *J* 5.5 Hz, 8-CH_3), 0.98 (3 H, d, *J* 7 Hz, 4-CH_3), 1.00 (3 H, s, 5-CH_3), 2.64 (2 H, s, 9-CH_2), 3.72 (s) and 3.76 (s) overlapped with 1 H, m (7 H, 2 × OCH_3 and H-3), and 6.70br (3 H, s, aromatic); with 1.04 : 1 molar ratio of Eu([$^2H_9$]fod)$_3$ to (18), δ 1.65 (3 H, d, *J* 5 Hz, 8-CH_3), 2.00 (3 H, s, 9-CH_3), 4.06 (6 H, s, OCH_3), 4.60br (1 H, m, H-4), 5.14 (3 H, s, 5-CH_3), 5.30 (3 H, d, *J* 7 Hz, 4-CH_3), 7.1 (1 H, m, H-1β*ax*), 9.62br (1 H, d, *J* 14 Hz, H-2β*eq*), and 14.3 (1 H, m, $W_{\frac{1}{2}}$ 8 Hz, H-3) (resonances from 9-CH_2 are not clearly visible at 1 : 1 molar ratio, being overlapped with other signals); *m/e* 360 (M^+, 4%), 191 (30), and 152 (100).

Treatment of the Epoxide (11) *with Boron Trifluoride*.—The epoxide (11) (27 mg) was treated with boron trifluoride–ether (0.1 ml) in anhydrous benzene (5 ml) at room temperature for 15 min. The resulting solution was diluted with diethyl ether (20 ml), extracted with aqueous sodium hydrogen carbonate, then brine, and dried. Evaporation left a residue which was submitted to column chromatography in benzene–ether (95 : 5). This afforded only one component, the *hydroxy-olefin* (14) (17 mg), m.p. 96—98° (from ethanol) (Found: M^+, 358.2513. $C_{23}H_{34}O_3$ requires *M*, 358.2508), $\nu_{max.}$ 3 600, 1 590, 1 490, and 1 465 cm^{-1}; δ 0.80 (3 H, d, *J* 6 Hz, 8-CH_3), 0.93 (3 H, s, 9-CH_3), 1.03 and 1.05 (6 H, each s, 4-CH_3), 2.58 and 2.80 (each 1 H, d, *J* 14 Hz, 9-CH_2), 3.46 (1 H, dd, *J* 8 and 3.5 Hz, H-3), 3.74 (6 H, s, OCH_3), and 6.68—6.76 (3 H, complex, aromatic); *m/e* 358 (M^+, 1.5%), 207 (100), 189 (56), 152 (9), and 151 (16).

Treatment of the Epoxide (12) *with Boron Trifluoride*.—The epoxide (12) (37 mg) was treated with boron trifluoride–ether (0.15 ml) in anhydrous benzene (5 ml) at room temperature for 15 min. Work-up as above afforded a product which gave two spots of similar polarity on t.l.c. (benzene–ether, 9 : 1). The mixture was separated by careful elution with benzene from silica gel. The less polar component, the oily *hydroxy-olefin* (15a) (7 mg) (Found: M^+, 358.2501. $C_{23}H_{34}O_3$ requires *M*, 358.2508), showed δ 0.81, 0.92, and 1.09 (each 3 H, s, tert. CH_3), 1.05 (3 H, d, *J* 6 Hz, 8-CH_3), 2.50 and 2.72 (each 1 H, d, *J* 13 Hz, 9-CH_2), 3.40 (1 H, dd, *J* 4 and 2 Hz, H-3), 3.72 and 3.74 (6 H, each s, OCH_3), 5.44 (1 H, m, H-6), and 6.60 (3 H, m, aromatic); *m/e* 358 (M^+, 6%), 207 (71), 189 (100), 152 (70), and 151 (20).

The more polar component, the oily *hydroxy-olefin* (15b) (13 mg) (Found: M^+, 358.2495) had δ 0.78 (3 H, d, *J* 6 Hz, 8-CH_3), 0.95 (3 H, s, 9-CH_3), 1.01 (3 H, s, 4α-CH_3), 1.08 (3 H, s, 4β-CH_3), 2.59 and 2.97 (each 1 H, d, *J* 14 Hz, 9-CH_2), 3.53 (1 H, dd, *J* 8 and 3 Hz, H-3), 3.71 and 3.75 (6 H, each s, OCH_3), and 6.72—6.81 (3 H, complex, aromatic); *m/e* 358 (M^+, 2%), 207 (100), 189 (50), 152 (16), and 151 (14).

Hydrogenation of Avarol Dimethyl Ether (6b).—The dimethyl ether (400 mg) in methanol was shaken with hydrogen over platinized charcoal (5%; 200 mg) for 5 h. Removal of catalyst and solvent left crystalline material (392 mg), which after recrystallization (three times) from ethanol gave *dihydroavarol dimethyl ether* (19), m.p. 147—149° (Found: C, 79.9; H, 10.1. $C_{23}H_{36}O_2$ requires C, 80.2; H, 10.5%); $[\alpha]_D$ −38.5 (*c* 1); δ(C_6D_6) 0.7 (3 H, d, *J* 6 Hz, sec. CH_3), 0.80 and 0.84 (6 H, each s, tert. CH_3), 1.05 (3 H, d, *J* 6 Hz, sec. CH_3), 2.70 (2 H, s, 9-CH_2), 3.43 and 3.50 (6 H, each s, OCH_3), and 6.53—6.75 (3 H, complex, aromatic); *m/e* 344 (M^+, 5.5%), 193 (16), and 152 (100).

Epoxidation of Friedel-3-ene.—A solution of friedel-3-ene (200 mg) in chloroform (20 ml) was treated with *m*-chloroperbenzoic acid (300 mg) and kept at room temperature for 24 h. Work-up as usual afforded a solid, which gave two spots of similar polarity on t.l.c. (benzene) in the ratio *ca.* 3 : 1. The mixture was separated by elution with benzene from a silica gel column. The less polar component was friedelan 3α,4α-epoxide (13a) (80 mg), m.p. 230—233° (from acetone), $[\alpha]_D$ +51° (lit.,[25] m.p. 234—236°, $[\alpha]_D$ +54°), δ(H-3) 2.81br (s, $W_{\frac{1}{2}}$ 7 Hz).

The more polar component was *friedelan* 3β,4β-*epoxide* (13b) (30 mg), m.p. 217—220° (from acetone), $[\alpha]_D$ +25° (Found: M^+, 426.3860. $C_{30}H_{50}O$ requires *M*, 426.3861). Apsimon *et al.*[25] obtained only friedelan 3α,4α-epoxide on reaction of friedel-3-ene with *m*-chloroperbenzoic acid at 0 °C; the α-epoxide was also obtained as a single diastereoisomer by Sengupta *et al.*[26] on reaction with monoperoxyphthalic acid at room temperature.

Lanthanide-induced shifts. (*a*) Compound (13a) showed methyl singlets at δ 0.82 (3 H), 0.95 (3 H), 0.99—1.01 (12 H), 1.06 (3 H, 5-CH_3), and 1.17 (3 H, 4-CH_3) and one-proton broad singlet at 2.82 ($W_{\frac{1}{2}}$ 7 Hz, H-3); with a 1 : 1 molar ratio of Eu([$^2H_9$]fod)$_3$ to (13a) methyl singlets were observed at δ 0.76, 0.84, 1.02, 1.23, 1.48, 2.07 (9-CH_3), 3.30 (5-CH_3), and 4.54 (4-CH_3), and other signals at 8.74 (1 H, dd, *J* 11 and 3 Hz, H-10) and 10.40br (1 H, s, H-3);

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' normalized ' $\Delta[\delta(Eu) - \delta(CDCl_3)]$ values for C-4, C-5, and C-9 methyl protons and H-3 and H-10 were 10.0, 7.3, 3.2, 22.6, and 21.7, respectively.

(*b*) Compound (13b) showed methyl singlets at δ 0.78 (3 H), 0.94 (3 H), 0.99 (12 H), 1.04 (3 H, 5-CH_3), and 1.16 (3 H, 4-CH_3) and a one-proton broad singlet at 2.86 ($W_{\frac{1}{2}}$ 3.5 Hz, H-3); with a 1 : 1 molar ratio of Eu([$^2H_9$]fod)$_3$ to (13b) methyl singlets were observed at 1.15, 1.18, 1.44, 1.53, 1.70, 1.86 (9-CH_3), 4.96 (4-CH_3), and 5.30 (5-CH_3) and one-proton broad singlet at 10.40 (H-3); ' normalized ' $\Delta[\delta(Eu) - \delta(CDCl_3)]$ values for C-4, C-5, and C-9 methyl protons and H-3 were 8.9, 10.0, 2.0, and 17.6, respectively.

^{13}C *N.m.r. Data for* cis-*Model Compounds*.—(*a*) Compound (21) showed δ_C 16.0, 17.5, 19.9, and 35.1 (quartets, CH_3), 17.5, 23.9, 29.1, and 29.7 (triplets, CH_2 of decalin skeleton), 37.4 and 45.3 (doublets, C-8 and C-10), 32.5 and 36.3 (singlets, C-5 and C-9), 64.9 (t, C-15), 126.4 (d, C-3), 145.2 (s, C-4), 37.0 (t, C-11), 35.2 (t, C-16), 30.3 (d, C-17), 40.1 (t, C-19), and 61.4 (t, C-20). Side-chain carbon signals were assigned by calculation in terms of the Grant rules.[27]

(*b*) Compound (22) showed δ_C 16.2, 16.4, 19.5, and 32.5 (quartets, CH_3), 18.1, 23.8, 28.5, and 29.5 (triplets, CH_2 of decalin skeleton), 39.3 and 46.0 (doublets, C-8 and C-10), 36.9 and 38.5 (singlets, C-9 and C-5), 123.3 (d, C-3), 139.3 (s, C-4), 37.4 (t, C-11 or C-19), 37.9 (t, C-19 or C-11), 155.3 (d, C-16), 142.9 (s, C-17), 193.6 (d, C-18), and 201.3 (d, C-20).

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