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NEW AVARONE AND AVAROL DERIVATIVES FROM THE MARINE SPONGE *DYSIDEA CINEREA*

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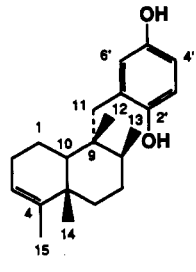
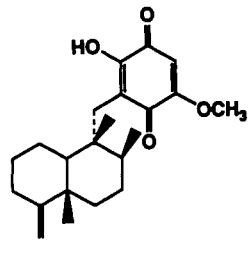
ABSTRACT.—Six new avarol and avarone derivatives, 3′-hydroxyavarone [**3**], 3′,6′-dihydroxyavarone [**4**], 6′-hydroxyavarol [**5**], 6′-acetoxyavarol [**6**], 6′-acetoxyavarone [**7**], and 6′-hydroxy-4′-methoxyavarone [**8**], are reported from the Red Sea sponge *Dysidea cinerea*. The structures of the new compounds were determined by spectroscopic data, mainly 1D and 2D nmr measurements. The absolute configurations of **5**, **6**, and **7**, and most likely also of **3**, **4**, and **8**, were established on the basis of cd measurements to be the same as that of avarol. Several of the new compounds are cytotoxic, possess antimicrobial activities, and have anti-HIV-1 reverse transcriptase activities; the most active is compound **8**.

In search of biologically active marine natural products we have found that the CH_2Cl_2 extract of *Dysidea cinerea* (Keller) (family Dysideidae, order Dictyoceratida) collected in the Gulf of Eilat, the Red Sea, possesses anti-HIV-1 reverse transcriptase activity. A strong inhibition of the HIV-1 reverse transcriptase enzymatic functions was tracked down to a fraction containing quinones. This report describes the structure of the new compounds, while the biological activity will be published elsewhere (16).

A variety of compounds having a quinone or a hydroquinone moiety attached to a sesquiterpene unit have been isolated from marine algae (1–3) and sponges (4–9, 13). Among the sponge metabolites are avarol [**1**] (5,6) and ilimaquinone [**2**] (8), which possess the rearranged drimane skeleton.



1



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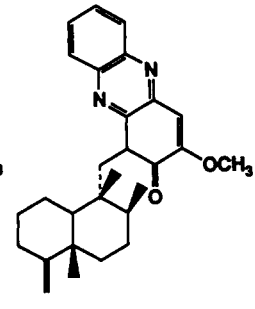

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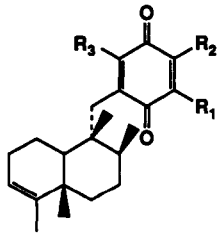
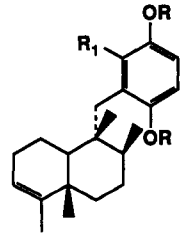
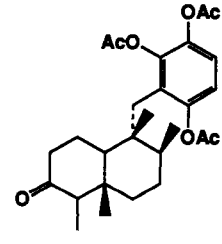


3 R_1=OH, R_2=R_3=H
4 R_1=R_3=OH, R_2=H
7 R_1=R_2=H, R_3=OAc
8 R_1=H, R_2=OMe, R_3=OH



5 R=H, R_1=OH
6 R=H, R_1=OAc
9 R=R_1=OAc



10

Specimens of the *D. cinerea* sponge were frozen shortly after collection at 15–20m near Ras Zaatir, in the Gulf of Eilat. The CH_2Cl_2 extract of the freeze-dried specimens was chromatographed in $CHCl_3$-MeOH-hexane (1:1:2) over Sephadex LH-20, then over a Si gel column eluted with hexane and increasing percentage of EtOAc, and again over Sephadex LH-20 prepared and eluted with $CHCl_3$-hexane (7:3) to afford six new compounds **3–8**. Starting from 30 g of one of the specimens of the dry sponge we obtained compounds **3** (100 mg), **4** (150 mg), **5** (100 mg), **6** (100 mg), **7** (20 mg), and **8** (55 mg) (the relative amounts changed remarkably from one collection to another).

Compound **3** showed hydroxyl (3400 cm^{-1}) and carbonyl (1640 cm^{-1}) absorptions in the ir spectrum and uv absorptions (MeOH) at 256 (ϵ 10200) and 284 (ϵ 3300) compatible with a hydroxyquinone structure (10). In its ^{1}H-nmr spectrum compound **3** showed four methyl signals, three singlets (δ 0.85, 1.00, and 1.53 ppm) and one doublet (δ 0.93), an AB quartet (δ 2.51 and 2.65 ppm, J = 13.5 Hz), a vinyl proton (δ 5.15), two aromatic protons (δ 6.76 and 6.75), and one exchangeable proton (δ 7.05). The ^{13}C-nmr spectrum (Table 1) showed 21 carbons including two carbonyls at 182.8 and 187.7 ppm, characteristic for a quinone (10), and six additional sp^2 carbons. The molecular formula $C_{21}H_{28}O_3$ (cims and elemental analysis) and the above-mentioned spectral features clearly indicated that compound **3** contains a hydroxyquinone moiety

TABLE 1. Comparison of ^{13}C-nmr Shifts for Compounds **1–8**.[a]

Carbon	Compound							
	3[b]	**4**[c]	**5**	**6**[d]	**7**	**8**[e]	**1**[f]	**2**
C-1	19.9	19.9	20.4	20.3	20.5	19.9	19.5	33.0
C-2	26.9	27.0	27.3	27.3	26.8	27.9	26.4	28.6
C-3	120.7	120.6	120.5	120.6	120.7	120.7	120.5	36.7
C-4	144.0	144.1	144.0	144.4	144.0	144.0	144.5	153.4
C-5	43.4	43.5	43.2	42.7	44.1	43.7	41.8	43.3
C-6	35.9	36.0	35.8	36.0	36.2	36.0	37.0	28.6
C-7	27.9	28.1	28.8	28.6	27.9	28.0	27.6	28.0
C-8	38.1	38.4	38.8	39.1	38.2	38.2	36.0	38.2
C-9	38.5	38.5	38.7	38.6	38.8	38.5	38.2	40.5
C-10	48.2	48.6	49.2	49.8	49.2	48.4	45.8	50.2
C-11	32.6	33.2	35.8	36.0	35.9	32.8	35.7	32.4
C-12	17.2	17.0	16.4	16.2	16.9	17.1	17.1	17.3
C-13	17.7	17.6	18.2	18.1	18.0	17.7	17.5	17.9
C-14	20.1	20.1	20.1	20.0	20.1	20.1	19.8	20.6
C-15	18.1	18.0	18.2	18.1	18.1	18.0	17.8	102.6
C-1′	120.7	121.8	113.2	116.2	120.7	120.8	129.1	117.4
C-2′	187.7	185.4	153.3	153.6	185.5	187.3	153.3	182.4
C-3′	152.7	152.7	120.6	119.6	137.5	109.0	111.1	161.8
C-4′	139.9	130.6	105.8	106.9	134.5	155.8	111.0	102.1
C-5′	182.8	181.8	131.3	132.1	181.0	178.5	153.1	182.4
C-6′	131.3	144.5	155.1	147.0	150.8	151.3	119.4	160.5

[a]Assignments of the carbon resonance lines were determined by CH-correlation experiments (J = 140, 10, and 7 Hz), in $CDCl_3$.

[b]Long range CH-correlations observed (C/H's): 3/2α,15; 4/10,15; 5/14; 6/10; 8/6β,11,13; 9/10,11,13; 10/6β,11,12; 11/12; 1′/11; 2′/4′, 6′/11; 3′/11; 5′/4′,6′.

[c]Long range CH-correlations observed (C/H's): 1′/11; 2′/4′,11; 3′/4′; 5′/4′; 6′/4′,11.

[d]Long range CH-correlations observed (C/H's): 1′/3′,11; 2′/4′,11; 5′/3′; 6′/4′,11.

[e]The reported carbon chemical shifts of the quinone moiety of isospongiaquinone are (C/δ_c): 1′/117.8, 2′/182.4, 3′/161.8, 4′/102.0, 5′/182.0 and 6′/153.4. The following CH-correlations were observed (C/H's): 1′/11; 2′/11; 3′/4′-OMe; 5′/3′; 6′/11.

[f]The ^{13}C-nmr chemical shifts are of avarol dimethyl ether.

linked to a sesquiterpene portion, similar to that of avarol [**1**] (1). Comparison of the ^{13}C-nmr data (Table 1) suggested for **3** the same sesquiterpene unit as in **1**. The proposed structure was also supported by the mass spectrum of **3** which showed, besides the $[M+3H]^+$ peak characteristic for quinones (11), dominant fragments at *m/z* 191 $[C_{14}H_{23}$ − the methylated decalin moiety$]^+$ and at *m/z* 140 $[C_7H_5O_3+3H$ − the quinone together with the benzylic methylene$]^+$. Further unequivocal proof for the suggested 3′-hydroxyavarone structure was obtained from long range CH correlations (shown in Table 1).

The latter experiment also established the 3′ position for the phenolic OH group by means of the C-3′ to H_2-11 correlation (the 6′ position for the hydroxyl being excluded as the two quinone protons appear as singlets in the nmr spectrum).

The relative stereochemistry of the chiral centers (C-5, -8, -9, and -10) was assigned as indicated on the basis of the almost identical ^{13}C-nmr spectrum of the sesquiterpene moiety of **3** and the same portion in avarol [**1**] (5,6). The stereochemistry was confirmed by an nOe experiment. Irradiation of Me-12 gave enhancements of H-1α (2%), Me-13 (2%), Me-14 (4%), and H-11 (4%). Irradiation of Me-13 gave an enhancement of H-7β (2%) and H-11 (3%), while irradiation of Me-14 gave enhancements of H-1β (4%), H-6β (7%), H-7β (3%), and Me-12 (5%).

The 5*S*,8*S*,9*R*,10*S* absolute configuration of avarol (6,12) is also suggested for compound **3** on the basis of the absolute configuration of compound **6**, as determined by cd measurements.

Comparison of the ^{1}H- and especially the ^{13}C-nmr spectra (Table 1) of compounds **3–8** clearly indicates that all six compounds have the same decalin moiety as avarol, with the differences between the various compounds being in the quinone portion.

Compound **4**, $C_{21}H_{28}O_4$, has an additional hydroxyl on the quinone moiety, *m/z* 153 $[C_7H_5O_4]^+$ (10%), the base peak being the decalin fragment at *m/z* 191 $[C_{14}H_{23}]^+$ (100%). A singlet at δ 6.73 and an additional exchangeable two-proton signal at 7.10 ppm could be seen in the ^{1}H-nmr spectrum. The distinction between three possible isomeric structures (the quinones with the single proton at the ortho, meta, or para position to the linking C-11 methylene) in favor of the 3′,6′-dihydroxy isomer was based on the long range CH correlations (shown in Table 1).

In the case of the 3′,4′- or 4′,6′-dihydroxy isomers, the above correlations required two to four bond correlations against the common two and three bond ones in the case of the proposed 3′,6′-isomer. Additional support for the proposed 3′,6′ structure came from the absence of a ^3J correlation between the single quinone proton and C-11, required in case of the 3′,4′-dihydroxy isomer, and from the formation of a different dimethoxy derivative from the one obtained from compound **8**, on methylation with CH_2N_2.

Compound **6**, $C_{23}H_{32}O_4$ *m/z* 373, $[MH]^+$ (9%), is slightly more polar than the other isolated compounds. The ^{1}H-nmr spectrum of **6** showed, in addition to the sesquiterpene portion, one acetate (δ 2.25 s) and two ortho-coupled aromatic protons (δ 6.80 d and 6.13 d, $J=8.7$ Hz). From the ^{13}C-nmr spectrum it was clear that compound **6** is a 1,2-disubstituted hydroquinone. Upon acetylation compound **6** afforded triacetate **9**, and oxidation with Ag_2O gave quinone **7** (9). The latter compound was identical with natural compound **7**.

Another closely related, more polar compound was **5**, $C_{21}H_{30}O_3$, *m/z* 330 $[M]^+$. According to the nmr data (Table 1 and Experimental) it was clear that **5** is deacetyl-**6**. Indeed, acetylation of **5** afforded the same triacetate **9** as **6**. Similarly to compounds **3** and **4**, compounds **5**, **6**, and **7** also gave strong *m/z* 191 peaks in the ci mass spectra. Compounds **6** and **7** also showed strong peaks at *m/z* 181 (21% and 26% respectively) for the acetoxy methylene aromatic unit $C_9H_9O_4$. In case of **6** the latter fragment is the

acetoxy hydroxyquinone moiety, and in case of **7** it is the quinone with an additional two protons. [The addition of 1–3 protons to quinones in the mass spectrometer is well known (11).] The base peak of **5** was *m/z* 140 $[C_7H_8O_3]^+$. The long range CH correlations measured for compound **6** (shown in Table 1) are in full agreement with the suggested structure.

Hydroboration of compound **9** followed by oxidative workup yielded the 3-keto derivative **10**. Compound **10** showed a negative Cotton effect at 290 nm for the $n\rightarrow\pi^*$ transition of the carbonyl, with the same sign and magnitude as the Cotton effect of the 3-keto derivative of avarol (6). Hence, the absolute configurations of **5**, **6**, and **7** have to be the same as that of avarol. If a common biogenetic route is assumed, the absolute configurations of **3**, **4**, and **8** are also the same as that of avarol.

The last compound, **8**, $C_{22}H_{30}O_4$, also possesses the same tricyclic carboxylic skeleton as compounds **1–7** (Table 1, Experimental). A singlet at δ 5.81, an exchangeable hydroxyl at δ 7.50 s, and a methoxyl at δ 3.80 s clearly pointed to a pentasubstituted quinone. As with compounds **3**, **4**, and **7**, the uv spectrum of the yellowish solution of **8** suggested that the major tautomer of all these compounds is the one with the ortho-hydroxy-para-quinone structure [rather than the tautomeric ortho-quinone, which should give a red solution with absorptions up to $\lambda = 450$nm (15)]. This, of course, does not exclude a possible condensation of these compounds with *o*-phenylenediamine. Indeed, compounds **4** and **8** as well as ilimaquinone [**2**] (obtained by us from a *Smenospongia* sp.) yielded, as judged by the development of a cherry-red color, an heterocyclic adduct by reaction with *o*-phenylenediamine. In the case of ilimaquinone, which was obtained in larger amounts, we have isolated the condensation product **11**. An nOe enhancement of 10% between the methoxy group and the single quinone proton in **8** determined their vicinal position. Thus, compound **8** has to be either the 6′-hydroxy-3′-methoxy or the 6′-hydroxy-4′-methoxy isomer. The first of the latter two compounds is a known marine natural product, isospongiaquinone (7). As the ^{13}C data of the quinone ring of isospongiaquinone differ substantially from those of compound **8** (Table 1), compound **8** has to be the 6′-hydroxy-4′-methoxy isomer. As with the former compounds, the nmr assignments were achieved from COSY and CH correlation experiments. The CH correlations (shown in Table 1) were in full agreement with the suggested substitution pattern of the quinone.

Small scale methylation of **8** with CH_2N_2 gave as expected a dimethoxyavarone (δ_{OMe} 3.73 s and 3.68 s).

Compounds **3**, **4**, and especially **8** (but not **5**, **6**, and **7**) showed activity as inhibitors of HIV-1 reverse transcriptase; these results are described more fully elsewhere (16). Avarol [**1**] was previously found to inhibit the growth of HIV; however, it was suggested that the mechanism of this activity does not involve the inhibition of the enzyme reverse transcriptase (14).

Compounds **3–8** are cytotoxic, the IC_{50}'s against P388 mouse leukemia cells being 0.6, 1.2, <0.6, 10, >20 μg/ml for compounds **3**, **4**, **6**, **7**, and **8**, respectively.

The compounds have also modest antifungal activity against *Candida albicans* (MIC's of 12.5, 50, 12.5 μg/ml were measured for **3**, **4**, and **6**, respectively).

EXPERIMENTAL

Ir spectra were recorded for solutions in $CHCl_3$ on a Perkin-Elmer Model 177, uv spectra for solutions in MeOH with a Varian Cary 219 spectrophotometer, and nmr spectra for solutions in $CDCl_3$ with a Bruker AM-360 spectrometer (TMS as internal reference) equipped with an Aspect 3000 computer. Mass spectra were measured with a Finnigan 4020 quadrupole spectrometer equipped with a data system. The cd curve was recorded with a Jasco 500C spectropolarimeter. Rotations were measured for solutions in MeOH.

COLLECTION AND EXTRACTION.—*D. cinerea* was collected at depths of 15–20 m near Ras Zaatir, in the Gulf of Eilat, the Red Sea. The specimens were frozen immediately after collection. The freeze-dried organism (30 g) was then extracted with CH_2Cl_2 to give after evaporation a gum (2 g). A voucher specimen was kept in our collection in Tel Aviv, TA-YK 2465.

COMPOUND **3**.—An oil: $[\alpha]^{25}D$ +45.0° (c = 0.060, $CHCl_3$); cims m/z $[M+3H]^+$ 331 (100%), $[C_{14}H_{20}O_3]^+$ 236 (10%), $[C_{14}H_{23}]^+$ 191 (61%), $[C_7H_8O_3]^+$ 140 (5%). Found C 76.60, H 8.42; $C_{21}H_{28}O_3$ requires C 76.79, H 8.59; ν max 3400 br, 2850, 1630, 1350 cm^{-1}; λ max (MeOH) 256 (10200), 284 (3300); δ_H ($CDCl_3$) 7.05 (s, 3′-O*H*, exchangeable by D_2O), 6.75 (s, H-4′), 6.75 (s, H-6′), 5.15 (brs, H-3), 2.65 (d, H-11, J = 13.5), 2.51 (d, H-11, J = 13.5), 2.04 (brt, H-1, J = 6.1), 2.02 (m, H-2), 1.85 (m, H-2) 1.63 (dt, H-6, J = 12.6, 3.1), 1.53 (4H, brs, H-1, Me-15), 1.36 (2H, m, H-7), 1.25 t (H-8, J = 6.2), 1.04 (m, H-10), 1.03 (m, H-6), 1.00 (s, Me-14), 0.93 (d, Me-13, J = 6.2), 0.85 (s, Me-12); δ_C ($CDCl_3$) see Table 1.

COMPOUND **4**.—An oil: $[\alpha]^{25}D$ +65.6° (c = 0.032, $CHCl_3$); cims m/z $[M-C_8H_{12}]^+$ 236 (45%), $[C_{14}H_{23}]^+$ 191 (100%), $[C_7H_5O_4]^+$ 153 (10%); ν max 3400–3300 br, 2850, 1640, 1350 cm^{-1}; λ max (MeOH) 256 (11400), 282 (8140); δ_H ($CDCl_3$) 7.1 (s, 2 × O*H*, exchangeble by D_2O), 6.73 (s, H-4′), 5.14 (brs, H-3), 2.60 (d, H-11, J = 13.3), 2.57 (d, H-11, J = 13.3), 1.98 (m, H-2), 1.96 (m, H-1), 1.88 (m, H-2), 1.65 (dt, H-6, J = 12.7, 3.2), 1.55 (m, H-1 overlaps with Me-15), 1.54 (s, Me-15), 1.38 (m, 2H, H-7), 1.30 (t, H-8, J = 6.2), 1.15 (m, H-6, overlaps with H-10), 1.13 (m, H-10), 1.01 (s, Me-14), 0.93 (d, Me, J = 5.9), 0.83 (s, Me-12); δ_C ($CDCl_3$) see Table 1.

COMPOUND **5**.—An oil: $[\alpha]^{25}D$ +60.0° (c = 0.02, MeOH); eims m/e $[MH]^+$ 330 (10%), $[C_{14}H_{23}]^+$ 191 (20%), $[C_7H_8O_3]^+$ 140 (100%); ν max 3600–3300 br, 2900 cm^{-1}; λ max (MeOH) 242 (2750), 294 (2200), 385 (500); δ_H ($CDCl_3$) 6.58 (d, H-4′, J = 8.4), 6.19 (d, H-3′, J = 8.4), 5.50 (brs, O*H*), 5.20 (brs, H-3), 4.70 (brs, O*H*), 4.50 (brs, O*H*), 1.55 s, 1.02 s, 0.90 s, 0.86 (d, J = 6.4) 4 × Me; δ_C ($CDCl_3$) see Table 1.

COMPOUND **6**.—An oil: $[\alpha]^{25}D$ +18.9° (c = 0.44, $CHCl_3$); cims m/z $[MH]^+$ 373 (9%), $[C_{21}H_{31}O_3]^+$ 331 (2%), $[C_{21}H_{31}O_2]^+$ 315 (6%), $[C_{14}H_{23}]^+$ 191 (100%), $[C_9H_9O_4]^+$ 181 (21%); ν max 3600–3300 br, 2900, 1720, 1425, 1175 cm^{-1}; λ max (MeOH) 298 (4000); δ_H ($CDCl_3$) 6.80 (d, H-3′, J = 8.7), 6.31 (d, H-4′, J = 8.7), 5.35 (brs, O*H*, exchangeable by D_2O), 5.15 (brs, H-3), 5.00 (O*H*, brs, exchangeable by D_2O), 2.75 (d, H-11, J = 14.2), 2.67 (d, H-11, J = 14.2), 2.25 (s, 6′-OAc), 2.03 (2H, m, H-2), 1.95 (m, H-1), 1.65 (m, H-8), 1.61 (ddd, H-6, J = 12.3, 4.3, 3.0), 1.56 (4H, m, H-1, overlaps with Me-15), 1.55 (brs, Me-15), 1.37 (m, H-10), 1.35 (2H, m, H-7), 1.12 (dt, H-6, J = 12.3, 8.5), 1.01 (s, Me-14), 0.89 (s, Me-12), 0.83 (d, Me-13, J = 6.5); δ_C ($CDCl_3$) see Table 1.

COMPOUND **7**.—An oil: $[\alpha]^{25}D$ −4.2° (c = 0.018, $CHCl_3$); cims m/z $[M+3H]^+$ 373 (12%), $[C_{21}H_{29}O_3]^+$ 329 (43%), $[C_{14}H_{23}]^+$ 191 (100%), $[C_9H_9O_4]^+$ 181 (26%); ν max 1720, 1630, 1350 cm^{-1}; λ max (MeOH) 250 (10300), 330 (550); δ_H ($CDCl_3$) 6.80 (d, H-3′, J = 10.1), 6.76 (d, H-4′, J = 10.1), 5.10 (brs, H-3), 2.62 (d, H-11, J = 13.5), 2.45 (d, H-11, J = 13.5), 2.30 s (6′-OAc), 2.0 (m, H-2), 1.87 (m, H-1), 1.63 (2H, m, H-8, H-6), 1.58 (4H, brs, H-1, Me-15), 1.36 (3H, m, H-6, H-7), 1.10 (dt, H-6, J = 12.3, 8.5), 1.00 (s, Me-14), 0.90 (d, Me-13, J = 5.6), 0.86 (s, Me-12); δ_C ($CDCl_3$) see Table 1.

COMPOUND **8**.—An oil: $[\alpha]^{25}D$ +75° (c = 0.040, $CHCl_3$); cims m/z $[M]^+$ 358 (4%), $[C_{14}H_{23}]^+$ 191 (30%), $[C_8H_{10}O_4]^+$ 170 (100%); ν max 3200, 2900, 1670, 1640, 1620, 1350, 1130 cm^{-1}; λ max (MeOH) 256 (12700), 294 (5400); δ_H ($CDCl_3$) 7.50 (brs, 6′-O*H*, exchangeable by D_2O), 5.81 (s, H-3′), 5.14 (brs, H-3), 3.80 (3H, s, 3′-OMe), 2.59 (d, H-11, J = 13.5), 2.52 (d, H-11, J = 13.5), 2.10 (2H, m, H-2), 2.0 (m, H-1), 1.65 (2H, m, H-8, H-6, not resolved), 1.54 (4H, brs, H-1, Me-15), 1.34 (3H, m, H-6, H-7), 1.09 (m, H-6), 1.05 (s, Me-14), 0.96 (d, Me-13, J = 5.7), 0.84 (s, Me-12); δ_C ($CDCl_3$) see Table 1.

OXIDATION OF COMPOUND **6** TO **7**.—To a solution of 8 mg of **6** in 40 ml of Et_2O was added Ag_2O (80 mg), and the heterogeneous mixture was stirred overnight at room temperature. The reaction mixture was filtered and the solvent evaporated to give 4 mg of a yellow oil. The ir, ms, and ^1H nmr of this product were identical with those of naturally occurring **7**.

ACETYLATION OF **5** AND **6** TO COMPOUND **9**.—A solution of 15 mg of **5** or **6** in 1 ml of pyridine and 1 ml of Ac_2O was allowed to stand overnight at room temperature, and then the mixture was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O and dried over $MgSO_4$. Evaporation gave 11 mg of pure **9**: cims $[C_{13}H_{14}O_6]^+$ 266 (1%), $[C_{14}H_{23}]^+$ 191 (100%); ν max 1760, 1210 cm^{-1}; δ_H ($CDCl_3$) 7.09 (d, H-4′, J = 8.9), 7.01 (d, H-3′, J = 8.9), 5.18 (brs, H-3), 2.68 (d, H-11, J = 13.5), 2.36 (d, H-11, J = 13.5), 2.26 (6H, s, 2 × OAc), 2.04 (3H, s, OAc), 1.85 (m, H-1), 1.66

(2H, m, H-8, H-6), 1.58 (4H, brs, H-1, Me-15), 1.34 (3H, m, H-6, H-7), 1.14 (m, H-6), 1.05 (3H, s, Me-14), 0.86 (3H, s, Me-12), 0.70 (3H, d, Me-13, $J = 6.3$).

OXIDATIVE HYDROBORATION OF **9** TO AFFORD COMPOUND **10**.—To a solution of triacetate **9** (20 mg) in dry Et_2O (2 ml), $NaBH_4$ (12 mg) and $ZnCl_2$ (3.5 mg) were added, followed by a solution of boron trifluoride-etherate (0.1 ml) in dry Et_2O (1 ml), and the 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 H_2O. The product was extracted with Et_2O, and the combined Et_2O extracts were washed with H_2O, aqueous $NaHCO_3$, and H_2O again, dried over $MgSO_4$, and evaporated to give ketone **10** (4 mg): cims $[M-C_2H_2O_2]^+$ 398 (2%), $[C_{13}H_{15}O_6]^+$ 267 (100%), $[C_{14}H_{23}O_2]^+$ 207 (20%); ν max 1760, 1705 cm^{-1}; δ_H ($CDCl_3$) 7.09 (d, H-4', $J = 8.9$), 7.01 (d, H-3', $J = 8.9$), 2.68 (d, H-11, $J = 13.5$), 2.46 (d, H-11, $J = 13.5$), 2.36 (6H, s, 2 × OAc), 2.26 (3H, s, OAc), 2.10 (3H, m, H-2, H-4), 1.90 (m, H-1), 1.66 (2H, m, H-8, H-6), 1.58 (m, H-1) 1.34 (3H, m, H-6, H-7), 1.14 (m, H-6), 1.05 (3H, s, Me-14), 0.89 (3H, d, Me-4, $J = 6.8$), 0.84 (3H, s, Me-12), 0.70 (3H, d, Me-13, $J = 6.3$); cd (MeOH) $[\theta_{290}]$ −4910.

COMPOUND **11**.—A solution of 10 mg of **2** (0.028 mmol) and 3.4 mg (0.031 mmol) of phenylene diamine in 10 ml MeOH was allowed to stand overnight at room temperature. The solvent was evaporated and the reaction mixture purified on a Sephadex LH-20 column eluted with hexane-$CHCl_3$ (3:7). Compound **11** was achieved as a cherry-red oil: cims $[M]^+$ 430 (1%), $[C_{17}H_{26}]^+$ 230 (46%), $[C_{13}H_{10}N_2]^+$ 194 (10%); $[C_{15}H_{25}]^+$ 205 (3%), $[C_{14}H_{23}]^+$ 191 (32%); λ max (MeOH) 230 (23740), 294 (8500), 320 (9200), 380 (2600), 460 (1080); δ_H (Me_2CO-d_6) 8.26 brs, 7.08 d ($J = 7.9$), 7.05 t ($J = 7.9$), 6.85 d ($J = 8.2$), 6.67 t ($J = 8.3$), 5.22 s, 4.39 s, 4.38 s, 2.47 d ($J = 13.9$), 2.37 d ($J = 13.9$), 1.10 s, 1.0 d ($J = 5.6$), 0.85 s.

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