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SIX NEW METABOLITES FROM THE BROWN ALGA *HALIDRYS SILIQUOSA* (PHAEOPHYTA, FUCALES)

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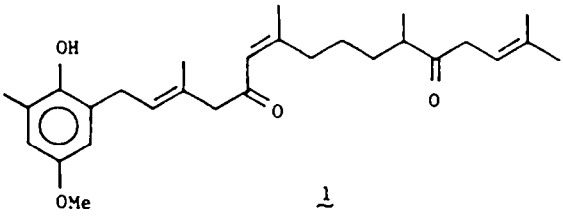
Abstract—Six monomethyl hydroquinols with oxygenated diterpene side chains have been isolated from the brown alga *Halidrys siliquosa*. We have isolated 5',12'-dioxohalidrol (**1**), 5',12'-dioxoisohalidrol (**2**), 12'α-hydroxy-5',13'-dioxohalidrol (**3**), 12'α-hydroxy-5',13'-dioxoisohalidrol (**4**), 12'β-hydroxy-5',13'-dioxoisohalidrol (**5**) and 5'-hydroxy-12-oxohalidrol (**6**).

In the search for bioactive compounds the Phaeophyta have been largely ignored as a source of new secondary metabolites. Sesquiterpenes and diterpenes and unusual C_{11} hydrocarbons have been isolated from algae belonging to the Dictyotaceae,[1] while the Fucaceae have yielded polyenes, polyprenylchromans and resorcinols.[2]

We now report the isolation of several related polyprenyl hydroquinol mono-methyl ethers from the brown alga *Halidrys siliquosa* (Order, Fucales, family Fucaceae) collected at Cumbrae, Scotland. Fresh *Halidrys siliquosa* was soxhlet extracted with methanol and the green oil obtained after removal of methanol partitioned between ethyl acetate and water. Chromatography of the lipophilic extract on Florisil followed by final purification by hplc led to the isolation of a group of related compounds 1–6.



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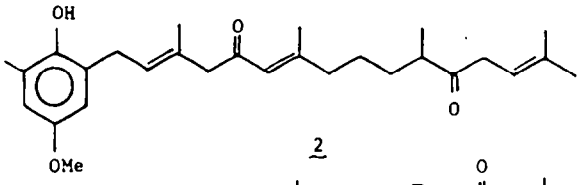

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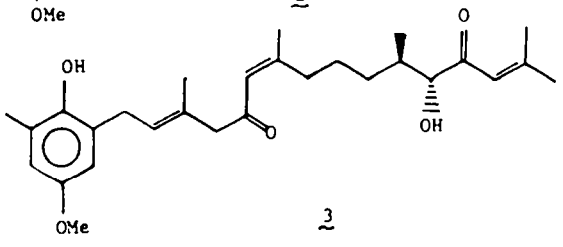

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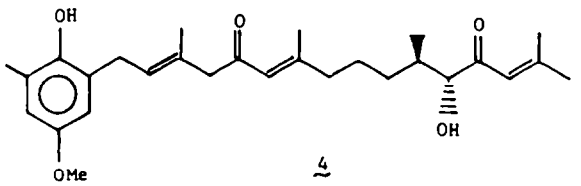

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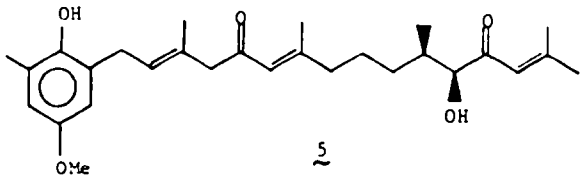

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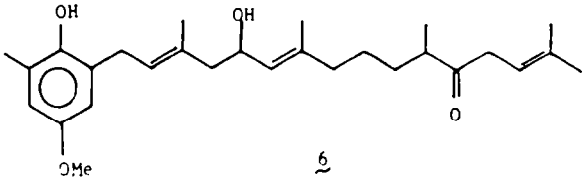
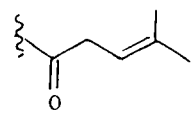


6

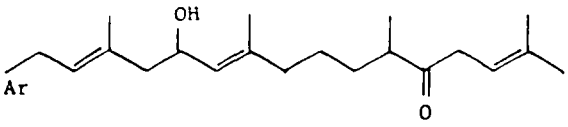
The allylic alcohol **6**, obtained as a colourless oil, $[\alpha]_D^{20} = +2.3°$ ($c = 8.9$, MeOH) had a molecular formula $C_{28}H_{42}O_4$ by high resolution mass spectroscopy. The UV spectrum ($\lambda_{max}^{MeOH} = 223$, 289 nm ($\epsilon = 9.030$, 3.270)) was consistent with the presence of a resorcinol or hydroquinol in which one of the OH's is methylated. The IR spectrum (ν_{max}, 1712, cm^{-1}) suggested the presence of a non-conjugated CO group, which was supported by the presence of a singlet at 215.9δ in the ^{13}C NMR spectrum.[4] This spectrum also contained a doublet at 67.8δ assigned to a secondary carbon bearing an OH group while the twelve resonances in the olefinic region were assigned to a tetrasubstituted aromatic ring and three trisubstituted double bonds. Resonances in the ^1H NMR spectrum of **6** at 1.47, 1.51, 1.62 and 1.64δ indicated the presence of four vinyl Me's groups, two of which, at 1.47 and 1.62δ sharpened on irradiation of a triplet at 5.46δ. This in turn was coupled to a two proton doublet at 2.95δ which had a chemical shift indicative of an allylic methylene α to a CO. These data were consistent with partial structure **7**.



7

A third vinyl Me resonance at 1.64δ was also broadened by coupling to the second olefinic triplet at 5.42δ, irradiation of which removed one of the couplings from the AB double doublets at 3.25 and 3.39δ.

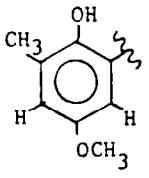
Irradiation of the methine proton at 4.46δ adjacent to the OH group caused the olefinic doublet at 5.20δ to coalesce to a broad singlet and removed a coupling from both sides of the AB system at 2.14 and 2.23δ leaving an AB quartet. A single proton sextet at 2.31δ was coupled to the secondary Me doublet at 0.92δ and to a methylene group which was shown by irradiation to form part of a chain of three methylene groups. On the basis of these irradiation experiments the terpenoid partial structure **8** was deduced.



8

The remaining signals in the ^{1}H NMR spectrum were associated with the aromatic ring substituents and confirmed the presence of Me and OMe groups, together with an AB system at 6.63 and 6.70δ (J = 3 Hz) ascribed to two *meta*-substituted protons. The substitution pattern around the aromatic ring could not be determined on the basis of UV and NMR data alone and was finally assigned by NOE experiments.

Irradiation of the OMe signal enhanced both aromatic protons by 8%, placing them both in an *ortho* relationship to the OMe group. Irradiation of the benzylic methylene produced a 15% enhancement in the proton at 6.63δ while a 15% enhancement of the second aromatic proton resulted from irradiation of the aromatic Me signal. On the basis of these experiments the partial structure **9** was assigned to the aromatic moiety.



9

The isomeric compounds **1** and **2**, isolated from a 1:1 mixture by HPLC, had several spectroscopic features in common with **6**. Isolated as colourless oils **1**, $[\alpha]_D^{20}$ = 10.7° (c = 15, CH_3OH) and **2** $[\alpha]_D^{20} = -1.2°$ (c = 11.3, CH_3OH) respectively, both gave molecular formulae of $C_{28}H_{40}O_4$ by high resolution mass spectroscopy. Their UV spectra contained maxima for the aromatic chromophore together with a maximum at 245 nm for an $\alpha\beta$-unsaturated ketone. This was supported by absorptions in the IR spectrum at 1678 and 1608 cm^{-1} as well as the 1712 cm^{-1} signal previously assigned in **6** to the saturated CO. The ^{13}C NMR spectrum contained two CO resonances at 214.9 and 200.5δ for **1** and 215.4 and 201.9δ for **2**, but no resonance characteristic of an allylic carbon bearing an OH group. The overall structures of **1** and **2** were assigned as oxidation products of **6** in which the 5′ OH group is replaced by a ketone.

The major differences between the ^{1}H NMR spectra of **1** and **2** were the changes in chemical shift of the vinyl Me C-19′ and the allylic methylene at C-9′. In **1** the vinyl Me resonates at 1.53δ and the methylene at 2.57δ, while the corresponding resonances in **2** were at 2.12δ and 1.77δ respectively. These differences in chemical shift are characteristic of the effects of steric compression between the carbonyl of an $\alpha\beta$-unsaturated ketone and the β substituent.[5] Thus the stereochemistry of the $\alpha\beta$ unsaturated ketone moiety was assigned as (Z) in **1** and (E) in **2**.

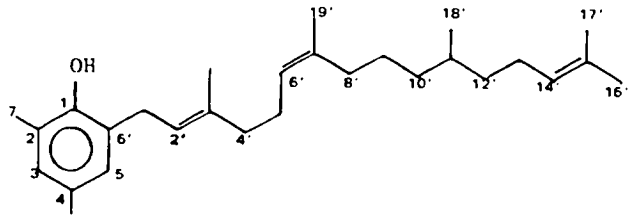
Compounds **3** and **4** formed a second isomeric pair isolated as colourless oils $[\alpha]_D^{20}$ = +49° (c = 4.7, CH_3OH) and +43° (c = 3.7, MeOH) respectively. Both contained an extra O atom, analysing as $C_{28}H_{40}O_5$ by high resolution mass spectroscopy. The UV spectra of **3** and **4** were similar to those of **1** and **2** although the extinction coefficients of the absorptions at 243 nm were higher, while the IR spectra contained no saturated CO absorption at *ca* 1712 cm^{-1}.

The presence of two $\alpha\beta$ unsaturated CO groups in each isomer was indicated by the ^{13}C spectra which contained resonances at 203.3 and 201.0δ for **3** and 203 and 201.6δ for **4** but no resonances for a saturated carbonyl. A doublet at *ca.* 80δ in each of the ^{13}C NMR's suggested the presence of a deshielded secondary OH. The ^{1}H NMR spectra both contained signals which could be assigned to the benzylic methylene at C-1′, placing the two CO's at C-5′ and C-13′. The methine proton at C-11′, a sextet in compounds **1**, **2** and **6** was further coupled by *ca* 2 Hz in compounds **3** and **4** to a one proton signal at 4.34 and 3.96δ in **3** and **4** respectively. These isomers were therefore formulated as the unusual α-hydroxy ketones with the OH in the C-12′ position. The chemical shifts of the C-19′ Me's, 1.66 and 2.17δ respectively; suggested that these compounds were also isomeric around the C-6′/7′ double bond with **3** the (Z) isomer and **4** the (E) isomer.

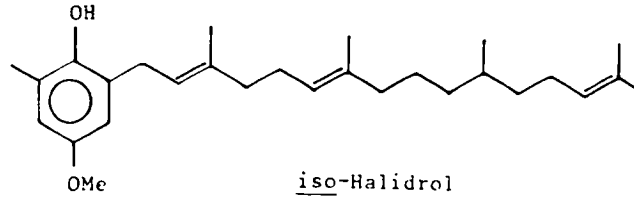
The remaining compound, **5**, $[\alpha]_D^{20} = -10°$ (c = 5, MeOH), was also isomeric with **3** and **4**. The only major difference between the ^{1}H NMR spectra of **4** and **5** was in the chemical shift of the secondary Me group at C-11′ which resonated at 0.71δ in the spectrum of **4** but was found at 1.11δ in that of **5**.

It was concluded that the difference between these two compounds was associated with the stereochemistry of the chiral centre at C-11′ or C-12′. The CD spectra of **3** and **4** both showed a positive Cotton effect, θ_{max}^{MeOH} = 318 nm, while **5** had a negative Cotton effect θ_{max}^{MeOH} = 308 nm. While it is not possible to obtain information about the absolute stereochemistry in such linear systems from these data, it does not appear unreasonable to conclude that the stereochemistry at either C-11′ or C-12′ has changed. On biosynthetic grounds it is more likely that the stereochemical variation is of the OH group rather than the secondary Me. Thus **4** and **5** form a diastereomeric pair. Removal of the chiral centre at C-12′ by oxidation and measurement of the CD spectra of the products would confirm the supposition that the optical centre at C-11′ had not altered. Unfortunately, under even very mild oxidation conditions using barium manganate,[4] solutions of **3**, **4** and **5** became bright orange yielding no isolable products.

Compounds **1**–**5** readily isomerised around the C-6′ double bond under acidic conditions, particularly **1** and **2** which rapidly equilibrated on silica gel or in $CDCl_3$ to a 1:9 mixture, the (E) isomer predominating. The (Z) isomers are therefore naturally occurring metabolites and while both isomers may occur in the alga the (E) isomers may be artifacts produced during isolation. The avoidance of acidic conditions during isolation could possibly



Halidrol



iso-Halidrol

Chemical shift of signals in ^1H NMR spectra of halidrol derivatives **1–6** (C_6D_6, δ (ppm from internal TMS))

Cpd.	CH_3O	$CH_3\phi$	C_3	C_5	C_1'	C_2'	C_4'	C_5'	C_6'	C_8'	C_9'	C_{10}'	C_{11}'	C_{12}'	C_{13}'	C_{14}'	C_{16}'	C_{17}'	C_{18}'	C_{19}'	$C_{2(}$
1	3.45	2.10	6.69	6.63	3.29	5.31	2.84	-	5.83	2.57	1.33	1.33 + 1.73	2.41	-	3.03	5.48	1.62	1.48	0.95	1.53	1.6
2	3.45	2.20	6.71	6.66	3.30	5.33	2.89	-	5.93	1.77	1.20	1.10 + 1.55	2.20	-	2.92	5.44	1.61	1.45	0.89	2.12	1.6
3	3.45	2.14	6.70	6.63	3.27	5.32	2.84	-	6.07	2.46 + 2.91	1.55	1.55 + 1.79	1.73	4.34	-	5.85	1.56	1.50	0.79	1.66	2.0
4	3.45	2.16	6.70	6.65	3.28 + 3.32	5.35	2.91	-	6.00	1.87	1.33	1.33 + 1.57	1.49	1.93	-	5.78	1.68	1.43	0.71	2.17	2.0
5	3.45	2.20	6.71	6.65	3.30	5.31	2.87	-	5.84	1.72	1.13	1.13 + 1.30	2.31	3.90	-	5.75	1.69	1.44	1.11	2.05	2.0
6	3.44	2.19	6.69	6.63	3.25 + 3.39	5.42	2.14 + 2.23	4.46	5.20	1.86	1.27	1.19 + 1.60	1.99	-	2.95	5.46	1.62	1.47	0.93	1.51	1.6

^{13}C NMR chemical shift in $^{12}CD_3OD$ (chemical shifts relative to TMS)

Compound					
1	2	3	4	5	6
214.9(s)	215.4(s)	203.3(s)	203.0(s)	203.3(s)	215.9(s)
200.5(s)	201.9(s)	201.0(s)	201.6(s)	201.6(s)	154.5(s)
161.1(s)	160.6(s)	161.7(s)	160.9(s)	161.1(s)	147.4(s)
154.2(s)	154.7(s)	159.3(s)	159.5(s)	159.8(s)	138.3(s)
147.2(s)	151.8(s)	154.4(s)	154.3(s)	154.5(s)	136.5(s)
135.9(s)	147.5(s)	147.3(s)	147.3(s)	147.6(s)	133.6(s)
131.3(s)	131.6(s)	131.6(s)	131.4(s)	131.8(s)	131.0(s)
129.9(s)	130.6(s)	130.4(s)	130.3(s)	130.4(s)	129.1(d)
128.6(d)	129.1(d)	128.8(d)	128.8(d)	129.1(d)	127.3(s)
127.1(s)	127.5(s)	127.3(s)	127.2(s)	127.3(s)	126.8(d)
123.9(d)	123.6(d)	124.0(d)	123.3(d)	123.6(d)	117.2(d)
117.0(d)	117.2(d)	120.9(d)	120.8(d)	121.3(d)	114.3(d)
114.3(d)	114.6(d)	114.4(d)	114.4(d)	114.7(d)	113.8(d)
113.2(d)	113.6(d)	113.4(d)	113.3(d)	113.7(d)	67.8(d)
55.8(t)	56.2(t)	79.9(d)	80.1(d)	82.4(d)	56.1(q)
55.8(q)	56.0(q)	55.9(t)	56.1(t)	56.2(t)	49.1(t)
46.1(d)	46.6(d)	55.9(q)	55.9(q)	56.2(q)	46.1(d)
41.7(t)	42.0(t)	36.6(d)	42.1(t)	42.3(t)	42.1(t)
34.2(t)	41.9(t)	34.7(t)	37.1(d)	37.7(d)	40.5(t)
33.6(t)	33.4(t)	34.5(t)	34.4(t)	31.1(t)	40.4(t)
29.7(t)	29.9(t)	29.8(t)	29.8(t)	30.2(t)	33.7(t)
26.1(t)	26.0(t)	27.9(q)	27.9(q)	28.4(q)	30.1(t)
25.8(q)	25.6(q)	26.6(t)	26.1(t)	26.3(t)	26.3(q)
25.4(q)	19.3(q)	25.6(q)	21.2(q)	21.7(q)	26.1(q)
18.0(q)	18.0(q)	21.3(q)	19.4(q)	19.9(q)	18.4(q)
16.9(q)	16.9(q)	17.0(q)	17.0(q)	17.5(q)	17.2(q)
16.6(q)	16.8(q)	16.6(q)	16.6(q)	17.5(q)	17.1(q)
16.6(q)	16.6(q)	13.6(q)	13.5(q)	17.1(q)	17.0(q)

lead to the identification of the (*Z*) isomer corresponding to **5**.

The numbering system used throughout conforms to the convention adopted by IUPAC–IUB for the nomenclature of quinones and hydroquinones with isoprenoid side-chains, which include members of the vitamin K and E and co-enzyme Q families.[5] As the aromatic substitution represented by compounds **1–6** has not previously been described we propose that the parent compound devoid of oxygenation in the terpenoid sidechain, in which the C-6′ double bond is (*Z*) and the C-2′ and C-14′ double bonds have the (*E*) configuration be named halidrol. Structures **2**, **4** and **5** in which the C-6′ olefin has the (*E*) configuration, we name *iso*-halidrols. Configurations at the various chiral centres have not been determined. Compounds **3**, **4** and **5** have been designated α and β at the C-12′ centre in order to show a change in stereochemistry.

EXPERIMENTAL

UV spectra were recorded on a Pye Unicam SP800 spectrophotometer and IR spectra on a Perkin–Elmer 157 spectrophotometer. Optical rotations were determined on a Perkin–Elmer 241 polarimeter with a one decimeter microcell and CD spectra were obtained using a Cary 61 spectrometer, both thermostated at 20°. Proton NMR spectra were recorded on Perkin–Elmer R12B and Brucker WH360 proton NMR spectrometers using deuterobenzene. Carbon spectra were run on the JEOL PFT100 in 100% ^{12}C methanol using a microprobe. Low and high resolution mass measurements were obtained using a Kratos MS50 mass spectrometer.

Collection and extraction. Halidrys siliquosa was collected at the Marine Biological Research Station, Isle of Cumbrae, Scotland. The frozen alga was shipped overnight to the Shell Laboratories where it thawed and 200 g (dry wt) was Soxhlet extracted with MeOH. The concentrated extract (15.2 g) was partitioned between EtOAc and water. The EtOAc extracts were combined, dried over $NaSO_4$, and the solvent removed to yield a bright green viscous oil (5.8 g).

Chromatographic separation. The crude extract was applied to a column (50 × 5 cm) of Florisil (100/120 mesh) and eluted using a solvent gradient starting with 50% ether in hexane and finishing with 10% MeOH in EtOAc. Fraction 2 (340 mg) contained predominantly **1** and **2** in a 1:1 ratio. These were separated by hplc on a 10 μ Lichrosorb diol column (20 × 1 cm) using 22% EtOAc in hexane as eluent to yield pure **1** (93 mg) and **2** (88 mg) as colourless oils. Fraction 3 (78 mg) contained only **3** and required no further purification. Fraction 5 (106 mg) was also pure, consisting of **4**. Fraction 4 (253 mg), a mixture of **3** and **4** in a 3:1 ratio, was further purified by hplc on the 10 μ Diol column using 22% EtOAc in hexane as eluent to yield **3** (150 mg) and **4** (40 mg). Fraction 6 (259 mg) contained predominantly **5** and **6** which were further purified by hplc on the Diol column eluted with 22% ethyl acetate in hexane. This yielded pure **5** (42 mg) and **6** (92 mg). All compounds were obtained as oils which failed to crystallise from a range of solvents.

5′,12′-Dioxo-halidrol (**1**). ν_{max} 3450, 1715, 1678 cm^{-1}; λ_{max}^{MeOH} = 222, 240, 288 nm (ϵ = 16,800, 14,600 4200); $\alpha_D^{20} = -10.7°$ (*c* = 15, MeOH); ^1H NMR (C_6D_6) δ 0.95 (d, 3H, *J* = 7 Hz), 1.33 (m, 3H), 1.48 (brs, 3H), 1.53 (brs, 3H), 1.62 (brs, 3H), 1.65 (brs, 3H), 1.73 (m, 1H), 2.19 (brs, 3H), 2.41 (sextet, 1H, *J* = 7 Hz), 2.57 (t, 2H, *J* = 7.5 Hz), 2.84 (s, 2H), 3.03 (d, 2H, *J* = 7 Hz), 3.29 (d, 2H, *J* = 7 Hz), 3.45 (s, 3H), 5.31 (brt, 1H, *J* = 7 Hz), 5.48 (brt, 1H, *J* = 7 Hz), 5.83 (brs, 1H). 6.63 (d, 1H, *J* = 3 Hz), 6.69 (d, 1H, *J* = 3 Hz); ^{13}C NMR ($^{12}CD_3OD$), δ, 214.9(s), 200.5(s), 161.1(s), 154.2(s), 147.2(s), 135.9(s), 131.3(s), 129.9(s), 128.6(d), 127.1(s), 123.9(d), 117.0(d), 114.3(d), 113.2(d), 55.8(t), 55.8(q), 46.1(d), 41.7(t), 34.2(t), 33.6(t), 29.7(t), 26.1(t), 25.8(q), 25.4(q), 18.0(q), 16.9(q), 16.6(q); mass spectrum, *m/e* 189 (100%), 69 (96.2), 191 (94.9), 440 (89.9, M^+), 151 (81.8), 109 (51.6), 206 (50.7), 95 (50.2). High resolution mass measurement, obs. 440.2927 ± 0.0001, $C_{28}H_{40}O_4$ requires: 440.2926.

5′,12′-Dioxo-iso-halidrol (**2**). ν_{max} 3450, 1714, 1680, 1608 cm^{-1}; λ_{max}^{MeOH} = 228 nm, (ϵ = 12,940, 2940); $\alpha_D^{20} = -1.24°$ (*c* = 11.3, MeOH); ^1H NMR (C_6D_6) δ 0.89 (brs, 3H), 1.10 (m, 1H), 1.20 (m, 2H), 1.45 (brs, 3H), 1.55 (m, 1H), 1.61 (brs, 3H), 1.68 (brs, 3H), 1.77 (t, 2H, *J* = 7.5 Hz), 2.12 (brs, 3H), 2.20 (brs, 3H), 2.22 (sextet, 1H, *J* = 7.7 Hz), 2.89 (s, 2H), 2.92 (brd, 2H, *J* = 7 Hz), 3.30 (d, 2H, *J* = 7 Hz), 3.45 (s, 3H), 5.33 (brt, 1H, *J* = 7 Hz), 5.44 (brt, 1H, *J* = 7 Hz), 5.93 (brs, 1H), 6.66 (d, 1H, *J* = 3 Hz), 6.71 (d, 1H, *J* = 3 Hz); ^{13}C NMR ($^{12}CD_3OD$) δ, 215.4(s), 201.9(s), 160.6(s), 154.7(s), 151.8(s), 147.5(s), 131.6(s), 130.6(s), 129.1(d), 127.5(s), 123.6(d), 117.2(d), 114.6(d), 113.6(d), 56.2(t), 56.0(q), 46.6(d), 42.0(t), 41.9(t), 33.4(t), 29.9(t), 26.0(t), 25.6(q), 19.3(q), 18.0(q), 16.9(q), 16.6(q); mass spectrum *m/e* M^+ 440 (27.1%), 189 (100%), 217 (83.8), 372 (52.3), 218 (49.6), 69 (42.4), 149 (37.9), 95 (34.8), 109 (34.1). High resolution mass measurement, obs. 440.2929 ± 0.0006, $C_{28}H_{40}O_4$ requires: 440.2926.

12′α-Hydroxy-5′,13′-dioxo-halidrol 4-methyl ether (**3**). ν_{max} 3450, 1680, 1610 cm^{-1}; λ_{max}^{MeOH} = 243, 289 nm (ϵ = 23,092, 3375); $[\alpha]_D^{20}$ = +49° (*c* = 4.7, MeOH); θ_{318}^{MeOH} = +3215°; ^1H NMR) C_6D_6) δ 0.79 (d, 3H, *J* = 7 Hz), 1.501.50 (brs, 3H), 1.55 (m, 3H), 1.56 (brs, 3H), 1.66 (brs, 3H), 1.79 (m, 1H), 1.99 (sextet d, 1H, *J* = 7, 7, 2 Hz), 2.08 (brs, 3H), 2.14 (brs, 3H), 2.46 (dt, 1H, *J* = 7, 12 Hz), 2.84 (s, 2H), 2.91 (dt, 1H, *J* = 7, 12 Hz), 3.27 (d, 2H, *J* = 7 Hz), 3.45 (s, 3H), 3.98 (d, OH, *J* = 5 Hz), 4.34 (dd, 1H, *J* = 2, 5 Hz), 5.32 (brt, 1H, *J* = 7 Hz), 5.85 (brs, 1H), 6.07 (brs, 1H), 6.63 (d, 1H, *J* = 3 Hz), 6.70 (d, 1H, *J* = 3 Hz); ^{13}C NMR ($^{12}CD_3OD$) δ 203.3(s), 201.0(s), 161.7(s), 159.3(s), 154.4(s), 147.3(s), 131.6(s), 130.4(s), 128.8(d), 127.3(s), 124.0(d), 120.9(d), 114.4(d), 113.4(d), 79.9(d), 55.9(q), 55.9(t), 36.6(d), 34.7(t), 29.8(t), 27.9(q), 26.6(t), 25.6(q), 21.3(q), 17.0(q), 17.0(q), 16.6(q), 13.6(q); mass spectrum *m/e* 83 (100%), 191 (26.1), 55 (26.1), 44, (25.8), 151 (19.9), 206 (16.4), 456 (16.1, M^+), 189 (14.9). High Resolution mass measurement; obs. 456.2875 ± 0.0005, $C_{28}H_{40}O_5$ requires 456.2873.

12′α-Hydroxy-5′,13-dioxoisohalidrol (**4**). ν_{max} 3450, 1680, 1610 cm^{-1}; λ_{max}^{MeOH} = 243, 290 nm (ϵ = 28,190, 3650); $[\alpha]_D^{20}$ = +43 (*c* = 3.7 MeOH); θ_{318}^{MeOH} = +3316°; ^1H NMR ($CDCl_3$) δ 0.71 (d, 3H, *J* = 7 Hz), 1.33 (m, 3H), 1.43 (brs, 3H), 1.57 (m, 1H), 1.68 (brs, 3H), 1.73 (sextet d, 1H, *J* = 7, 7, 2 Hz), 1.87 (t, 2H, *J* = 7 Hz), 2.06 (brs, 3H), 2.16 (brs, 3H), 2.17 (brs, 3H), 2.91 (brs, 2H), 3.28 (AB of ABX system, 1H), 3.32 (AB of ABX system, 1H), 3.96 (dd, 1H, *J* = 2, 5 Hz), 4.07 (d, OH, *J* = 5 Hz), 5.35 (brt, 1H, *J* = 7 Hz), 5.78 (brs, 1H), 6.00 (brs, 1H), 6.65 (d, 1H, *J* = 3 Hz), 6.70 (d, 1H, *J* = 3 Hz), ^{13}C NMR ($^{12}CD_3OD$) δ 203.0(s), 201.6(s), 160.0(s), 159.5(s), 154.3(s), 147.3(s), 131.4(s), 130.3(s), 128.8(d), 127.2(s), 123.3 (d), 120.8(d), 114.4(d), 113.3(d), 80.1(d), 56.1(t), 55.9(q), 42.1(t), 37.1(d), 34.4(t), 29.8(t), 27.9(q), 26.1(t), 21.2(q), 19.4(q), 17.0(q), 16.6(q), 13.5(q); mass spectrum, *m/e* 456 (11.4%, M^+) 83 (100%), 55 (26.6), 41 (21.1), 43 (16.0), 151 (14.5), 44 (14.1), 69 (13.1), 67 (13.0). High resolution mass measurement, obs. 456.2877 ± 0.0003, $C_{28}H_4O_5$ requires 456.2875.

12′β-Hydroxy-5,13′-dioxoisohalidrol (**5**). ν_{max} 3450, 1680, 1610 cm^{-1}; λ_{max}^{MeOH} = 218, 242, 289 nm (ϵ = 19,460, 33,440, 3160); $[\alpha]_D^{20} = -9.6°$ (*c* = 5, MeOH); $\theta_{308}^{MeOH} = -1641°$; ^1H NMR ($CDCl_3$) δ 1.11 (d, 3H, *J* = 7 Hz), 1.13 (M, 3H), 1.30 (m, 1H), 1.44 (brs, 3H), 1.49 (sextet d, 1H, *J* = 7, 7, 2 Hz), 1.69 (brs, 3H), 1.72 (t, 2H, *J* = 7 Hz), 2.05 (brs, 3H), 2.06 (brs, 3H), 2.20 (brs, 3H), 2.87 (s, 2H), 3.30 (d, 2H, *J* = 7 Hz), 3.45 (s, 3H, 3.90 (dd, 1H, *J* = 2, 5 Hz), 3.94 (d, OH, *J* = 5 Hz), 5.31 (brt, 1H, *J* = 7 Hz), 5.75 (brs, 1H), 5.84 (brs, 1H), 6.65 (d, 1H, *J* = 3 Hz), 6.71 (d, 1H, *J* = 3 Hz), ^{13}C NMR ($^{12}CD_3OD$) δ, 203.3(s), 201.6(s), 161.1(s), 159.8(s), 154.5(s), 147.6(s), 131.8(s), 130.4(s), 129.1(d), 127.3(s), 123.6(d), 121.3(d), 114.7(d), 113.7(d), 82.4(d), 56.2(t), 56.2(q), 42.3(t), 37.7(d), 31.3(t), 30.2(t), 28.4(q), 26.3(t), 21.7(q), 19.9(q), 17.5(q), 17.1(q); mass spectrum *m/e* 83 (100%), 55 (39.0), 191 (31.6), 41 (26.3), 151 (26.3), 456 (22.7, M^+), 43 (21.5), 206 (20.3). High resolution mass measurement, obs. 456.2871 ± 0.0001, $C_{28}H_4O_5$ requires 456.2875.

5′-Hydroxy-12′oxohalidrol (**6**). ν_{max} 3450, 1712, 1608 cm^{-1}; λ_{max}^{MeOH} = 223,290 nm (ϵ = 9034, 3269); $[\alpha]_D^{20}$ = +2.3° (*c* = 8.9, MeOH), ^1H NMR (C_6D_6) δ 0.93 (d, 3H, *J* = 7 Hz), 1.19 (m, 1H), 1.27 (m, 2H), 1.47 (brs, 3H), 1.51 (brd, 3H, *J* = 1.2 Hz), 1.60 (m, 1H), 1.62 (brs, 3H), 1.64 (brs, 3H), 1.86 (t, 2H, *J* = 7 Hz), 2.14 (dd, 1H, *J* = 5, 13 Hz), 2.19 (brs, 3H), 2.23 (dd, 1H, *J* = 5, 13 Hz), 2.23 (dd, 1H, *J* = 5, 13 Hz), 2.31 (sextet, 1H, *J* = 7, 7 Hz), 2.95 (d, 2H, *J* = 7 Hz), 3.25 (dd, 1H, *J* = 6, 15 Hz), 3.99 (dd, 1H, *J* = 8, 15 Hz),

3.44 (s, 3H), 4.46 (td, 1H, J = 5, 8, 8 Hz), 5.20 (brd, 1H, J = 8 Hz), 5.42 (brt, 1H, J = 7, 7 Hz), 5.46 (brd, 1H, J = 7 Hz), 6.63 (d, 1H, J = 3 Hz), 6.69 (d, 1H, J = 3 Hz); ^{13}C NMR ($^{12}CD_3OD$) δ, 215.9(s), 154.5(s), 147.4(s), 138.3(s), 136.5(s), 133.6(s), 131.0(s), 129.1(d), 127.3(s), 126.8(d), 117.2(d), 114.3(d), 113.8(d), 67.8(d), 56.1(q), 49.1(t), 46.1(t), 42.1(t), 40.4(t), 33.7(t), 30.1(t), 26.3(q), 26.1(q), 18.4(q), 17.2(q), 17.1(q), 17.0(q); mass spectrum *m/e* 191 (100%), 424 (78.6), 151 (68.9), 41 (51.8), 189 (43.9), 69 (35.9), 147 (31.3), 229 (27.9); High resolution mass measurement: obs. 424.2978 ± 0.0002, $C_{28}H_{40}O_3$ ($M^+ - 18$) requires 424.2977.

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