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New Antineoplastic Prenylhydroquinones. Synthesis and Evaluation

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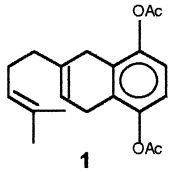
Abstract—Several prenylhydroquinones have been prepared through Diels–Alder condensation, further functionalized or degraded chemically and then evaluated for their cytotoxic activity against some neoplastic cultured cell lines. A number of them have shown IC_{50} values under the μM level.

Introduction

In previous related papers it has been reported, the synthesis and evaluation of the cytotoxic/antineoplastic activity of a number of terpenyl naphthoquinones/hydroquinones and terpenylanthraquinones against cultured cells of P-388 murine leukemia, A-549 human lung carcinoma, HT-29 human colon carcinoma and Mel-28 human malignant melanoma neoplastic systems.[1,2] Most of the compounds tested showed IC_{50} values in the range of avarol and avarone, benzenoid hydroquinone/quinone-sesquiterpenyl derivatives, isolated from the sponge *Dysidea avara* and generally considered as prototypes, due to their cytotoxicity against several types of tumoral cells.[3–7] However, certain compounds of those synthesized and evaluated by some of us, resulted in being several times more potent than those of natural origin. The results of the evaluation showed that naphthoquinone derivatives displayed higher antineoplastic potency than benzoquinone and anthraquinone derivatives and also that the size and functionality of the terpenyl fragment was important for the activity. In the first instance, some of the compounds tested, showed a certain degree of selectivity against murine leukemia and lung carcinoma systems,[1,2] but when they were submitted to the wider evaluation screening of the NCI, Bethesda, USA, a greater selectivity against most cell lines of renal carcinoma, was observed.

In order to get more information, which allowed us to obtain better structure–activity relationships for this kind of compound, a new series of derivatives have been designed, synthesized and evaluated to analyze the effect of the unsaturation degree of the side chain and the cycloaliphatic ring on the bioactivity. In this paper we wish to report the synthesis and bioactivity behavior of a family of derivatives from the prenylhydroquinone **1**, prepared through hydrogenation and further chemical transformations.



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Results and Discussion

Chemistry

The new prenylhidroquinone derivatives were prepared using compound **1** as the starting substrate. It was conveniently obtained from the Diels–Alder condensation between α-myrcene and *p*-benzoquinone, followed by acetylation.[1,2]

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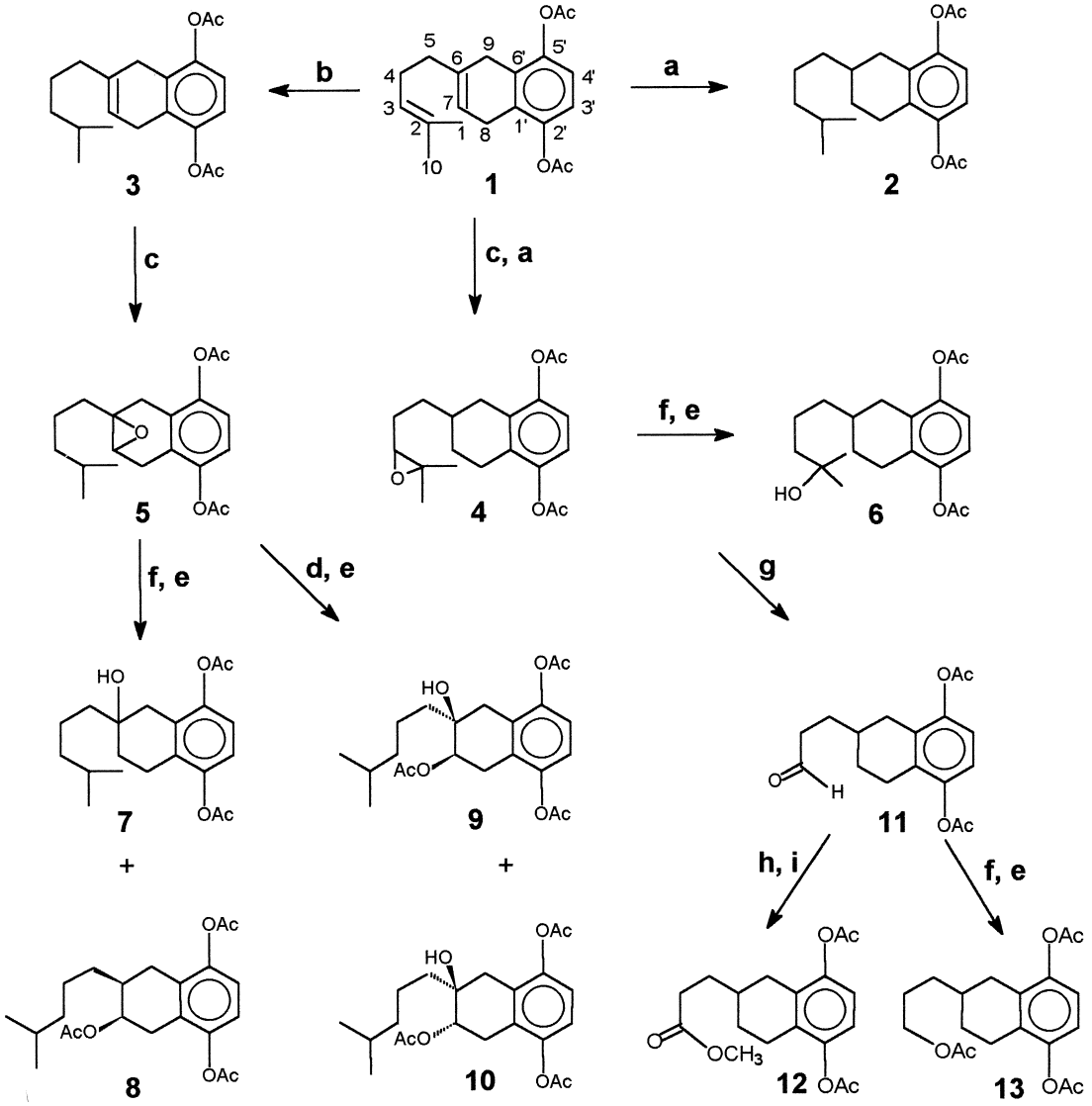
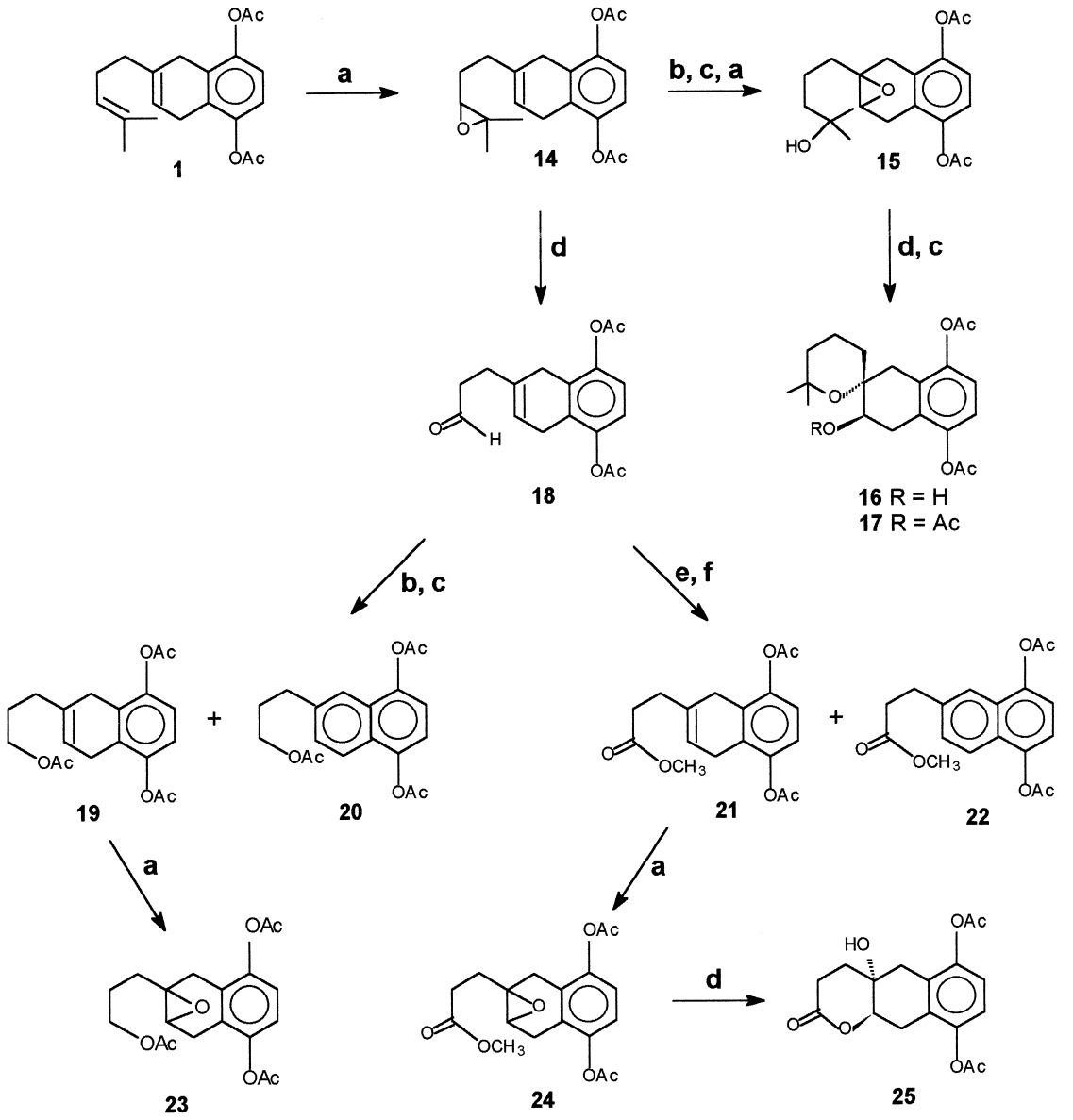
One part of the chemical transformations are summarized in Scheme 1. The monoterpenyl derivative **1**, was fully and selectively hydrogenated in the presence of Pd/C or $Pd/CaCO_3$ as catalysts, to afford **2** and **3**, respectively. The functionality of both the side chain of **1** and the aliphatic ring of **3** were changed through epoxidation with *m*-chloroperbenzoic acid (MCPBA) to give the epoxides **4** and **5**. The lithium aluminum hydride (LAH) reduction of **4** and **5** followed by acetylation, afforded the expected tertiary alcohols **6**, **7** and the triacetate **8**. Also, the acid hydrolysis of **5** by prolonged treatment with HCl, yielded the expected isomeric diols with the saturated side chain, that were isolated as their monoacetylated derivatives **9** and **10**. The relative *cis* configuration in compound **9** was assigned on the basis of the double doublet multiplicity observed for the absorption of the hydrogen atom geminal to the acetate group, while the triplet observed for the same hydrogen in the spectrum of **10**, was in agreement with the relative *trans* configuration assigned to the last compound. Treatment of the epoxide **4** with periodic acid resulted in the formation of the aldehyde **11**, further oxidized with pyridinium dichromate (PDC) to the corresponding carboxylic acid, which was isolated as its methyl ester **12**. Finally, LAH reduction of the aldehyde **11** afforded the expected primary alcohol, also isolated as its acetate **13**. Compounds **3**–**13** are new prenylhydroquinone derivatives with a saturated or degraded side chain.

Other series of compounds were prepared starting from the epoxide derivative **14**, previously described.[2] The transformations performed are summarized in Scheme 2. Compound **14** was readily reduced with LAH to the corresponding tertiary alcohol, which on acetylation and further epoxidation, gave compound **15**, but the attempts to cleave directly the epoxide ring of **15** by treatment with periodic acid, resulted only in the formation of the hydroxy-spiroether **16**, which on acetylation afforded the acetate **17**. As it was previously reported,[2] the side chain of epoxide **14** could be oxidized



Scheme 1. The synthesis of some prenylhydroquinones derivatives. (a) H_2, Pd/C, AcOEt, rt, 8 h, 96%; (b) H_2, $Pd/CaCO_3$, AcOEt, rt, 24 h, 97%; (c) MCPBA, CH_2Cl_2, $NaHCO_3$, rt, 4 h, 46–62%; (d) HCl, *t* BuOH, H_2O, rt, 18 h, 78%; (e) Ac_2O, Py, rt, o.n., 43–71%; (f) $LiAlH_4$, Et_2O, rt, 6–8 h, 43–49%; (g) H_5IO_6, THF, H_2O, rt, 2 h, 62%; (h) PDC, DMF, rt, 24 h, 64%; (i) CH_2N_2, Et_2O, rt, 30 min, 95%.



Scheme 2. The synthesis of other hydroquinone derivatives. (a) MCPBA, $NaHCO_3$, CH_2Cl_2, rt, 1 h, 75–88%; (b) $LiAlH_4/Et_2O$, rt, 6 h, 95%; (c) Ac_2O, Py, rt, o.n., 90%; (d) $H_5IO_6/THF/H_2O$, rt, 2–24 h, 59–89%; (e) PDC, DMF, rt, 24 h, 80%; (f) CH_2N_2, Et_2O, rt, 30 min, 95%.

and degraded to the aldehyde **18** with periodate/formic acid or periodic acid and this substance was used to prepare the rest of the compounds indicated in Scheme 2. When **18** was reduced with LAH to the corresponding primary alcohol and then acetylated, the expected triacetate **19** was formed as the main product, together with the fully aromatized side product **20**, probably due to the spontaneous auto-oxidation of the intermediate hydroquinone derivative. On the other hand, the successive oxidation and methylation of **18** with PDC and diazomethane, resulted in a mixture of the respective methyl ester **21** and the fully aromatized ester **22**. The treatment of **19** and **21** with MCPBA gave the expected epoxides **23** and **24**, respectively. Finally, when **24** was treated with periodic acid, the hydroxylactonic derivative **25** was obtained.

Those compounds containing disymmetric centers are racemic and no attempts have been made at this stage for attaining their enantiomeric resolution. The principal ^1H NMR and ^{13}C NMR data are shown in Tables 1 and 2, while their IR absorptions and other physical data are reported in the experimental part.

Bioactivity

Most of the compounds prepared, were evaluated for determining their antineoplastic activities against culture cells of P-388, A-549, HT-29 and Mel-28, by a reported standard procedure.[8] The results are shown in Table 3 and cytotoxicity data for avarol[6,7] is also included for comparison purposes.

From these data, it can be observed that, with the exception for compound **17**, the IC_{50} cytotoxicity values ranged between 0.3 and 15.1 μM and compounds **2**, **3**, **20** and **22** showed to be several times more potent than avarol. Also, the majority of compounds tested showed

Table 1. ^{1}H NMR data of compounds **2**–**25**

H	2	3	4	5	6	7	8	9	10	11	
1-10	0.89d (6.6)	0.89d (6.6)	1.30d (6.7)	0.89d (6.5)	1.22s	0.87d (6.6)	0.89d (6.6)	0.91d (5.5)	0.88d (6.5)		
3	—	—	—	—	—	—	—	—	—	9.80t (1.5)	
5	—	2.07t (7.6)	—	2.83m	—	—	—	—	—	—	
7	—	5.55s	—	3.27m	—	—	—	5.34dd (4.4, 3.3)	5.09t (4.7)	—	
8	—	3.10d (5.2)	—	—	—	—	—	—	—	—	
9	—	3.21bs	—	—	—	—	—	—	—	—	
3′-4′	6.88s	6.93s	6.87s	6.93s	6.87s	6.91s	6.91s	6.99s	6.95s	6.88s	
Ac	2.31s	2.31s	2.29s	2.31s	2.30s	2.31s	2.31s	2.30s	2.30s	2.30s	
Ac	2.32s	2.34s	2.30s	2.33s	2.31s	2.32s	2.31s	2.34s	2.32s	2.31s	
Ac	—	—	—	—	—	1.93s	—	2.03s	2.03s	—	

H	12	13	16	17	19	20	21	22	23	24	25
1-10	—	—	1.27s	1.16s	—	—	—	—	—	—	—
3	—	4.08t (6.6)	—	—	4.09t (6.6)	4.14t (6.6)	—	—	4.11m	—	—
4	2.42t (7.2)	—	—	—	1.81m	2.02m	2.47m	3.13t (7.6)	1.80m	2.47t (7.3)	—
5	—	—	—	—	2.11t (7.9)	2.86t (7.2)	2.47m	2.71t (8.0)	1.80m	2.13m	—
7	—	—	3.86m	5.25t (4.4)	5.58t (1.4)	7.40dd (1.7,7.1)	5.57t (1.4)	7.40dd (1.7,8.6)	3.00m	3.01m	4.22m
8	—	—	—	—	3.15m	7.80d (8.7)	3.15m	7.80d (8.6)	3.00m	3.01m	—
9	—	—	—	—	3.15m	7.63d (1.7)	3.15m	7.66d (1.6)	3.00m	3.01m	—
3′-4′	6.87s	6.87s	6.92s	6.99s	6.93s	7.20s	6.92s	7.21s	6.93s	6.93s	6.97s
Ac	2.29s	2.29s	2.30s	2.30s	2.31s	2.45s	2.30s	2.45s	2.31s	2.30s	2.31s
Ac	2.31s	2.31s	2.31s	2.34s	2.34s	2.46s	2.31s	2.48s	2.33s	2.32s	2.32s
Ac	—	2.05s	—	2.03s	2.05s	2.06s	—	—	2.05s	—	—
MeO	3.68s	—	—	—	—	—	3.67s	3.68s1	—	3.70s	—

a certain degree of selectivity, up to 10 times in the case of compounds **20** and **22**, against the murine leukemia P-388 system.

From these results it can be observed that a higher saturation degree of the terpenic part, including the side chain and the ring, is important for the activity (compounds **2**, **3**). It is also confirmed that the aromatization of the ring fused to the quinone moiety (**20**, **22**), as it was previously reported,[1,2] improves the cytotoxic potency. On the other hand, the introduction of a hydroxyl group on the cyclohexane ring or in the side chain results in a decrease of the antineoplastic potency. Further studies in this sense are currently in progress.

Experimental

IR spectra were recorded on a Perkin–Elmer FT IR 1600 spectrophotometer as film over sodium chloride discs. NMR spectra were obtained at 200 MHz for ^{1}H and 50 MHz for ^{13}C in deuterochloroform using TMS as internal reference, on a Bruker AC-200 spectrophotometer. Chemical shift values are expressed in ppm followed by multiplicity and coupling constants J in Hz. Column chromatography (CC) was performed on silicagel 60, 230–400 mesh ASTM (Merck no 109385). Melting points were determined in a Electrothermal Digital Melting Point apparatus and are uncorrected.

Chemistry procedures

The following reactions were performed according to previously reported procedures.

Epoxidation with *m*-chloroperbenzoic acid (MCPBA) in dichlorometane and in the presence of $NaHCO_3$; reduction of aldehydes or epoxides with lithium aluminum hydride (LAH) in dry ether; acid hydrolysis of epoxides with $HCl/H_2O/t$BuOH; acetylation with acetic anhydride/pyridine; aldehyde oxidation with pyridinium dichromate (PDC) in dimethylformamide (DMF) and methylation of carboxylic acids with CH_2N_2/ether.[2,9]

The selective catalytic hydrogenation of the chain double bond was performed by bubbling H_2 during 17 h into a solution of 3.0 mmol of the compound in 30 mL of EtOAc containing 300 mg of 5% $Pd/CaCO_3$. After separation of the catalyst the solvent was evaporated and the reaction product was purified by CC using hexane/EtOAc in variable proportions as eluent . The fully catalytic hydrogenation of both double bonds was performed in the same way, changing the catalyst to 5% Pd/C.

Epoxides were degraded treating 0.6 mmol of the compound in 10 mL THF with a solution of 1.2 mmol of H_5IO_6 in 6.0 mL of H_2O, at room temperature. The progress of the reaction was monitored by TLC and after completation, the reaction mixture was diluted with 50 mL of ether. The organic layer was washed with aqueous 5% $Na_2S_2O_3$ (3×30 mL), water until pH 7 of the aqueous layer and dried over Na_2SO_4. After evaporation of the solvent, the reaction product was purified by CC using hexane/EtOAc in variable proportions as eluent.

Identification

Using these reactions, the following new compounds were prepared.

Compound 2. Obtained by fully catalytic hydrogenation of **1** (96%); mp 74–75 °C; IR cm^{-1} 2925, 2868, 1763,

Table 2. ^{13}C NMR data of compounds **2**–**25**

C	2	3	4	5	6	7	8	9	10	11	12
1-10	22.7	22.7	18.3	22.6	29.3	22.6	22.6	22.6	22.5	—	—
2	27.9	27.9	56.3	27.9	70.9	33.5	32.2	27.7	27.9	—	—
3	39.1	25.2	64.4	22.5	44.0	29.8	28.0	34.4	33.0	202.3	174.0
4	30.3	37.3	30.2	36.6	27.8	35.6	32.2	38.8	36.7	27.6	32.5
5	22.9	38.6	32.7	38.7	21.5	36.7	39.4	39.4	39.4	23.4	27.5
6	36.5	116.6	26.4	57.0	36.6	27.8	69.8	68.7	70.6	41.4	31.2
7	23.7	134.1	27.7	56.4	23.6	81.3	22.8	71.0	72.0	32.5	23.5
8	24.6	25.2	32.9	24.7	30.2	39.0	36.3	21.1	20.0	28.1	29.9
9	32.6	27.5	32.8	26.9	32.8	38.9	41.6	27.3	26.8	29.4	31.6
1′	131.2	128.7	130.7	126.7	131.0	128.5	129.9	127.0	128.0	130.3	130.5
2′	146.6	146.1	146.6	146.4	146.5	146.2	147.0	146.2	146.6	146.5	146.5
3′	119.5	119.9	119.6	120.3	119.5	119.8	119.9	120.5	120.4	119.7	119.6
4′	119.4	119.8	119.6	120.2	119.6	120.0	119.9	120.4	120.3	119.7	119.7
5′	146.6	146.1	146.6	146.5	146.6	146.8	146.4	146.6	146.6	146.5	146.5
6′	131.2	128.6	130.9	125.8	131.0	129.8	129.1	126.3	127.2	130.7	130.8
Ac	169.3	196.3	162.2	168.9	169.2	169.1	169.2	168.9	169.2	169.2	169.2
Ac	20.6	20.8	20.8	20.8	20.8	20.8	20.8	20.9	20.8	20.8	20.8
Ac	169.3	169.3	162.2	168.9	169.3	169.2	169.2	169.0	169.2	169.2	169.2
Ac	20.6	20.9	20.8	20.8	20.8	20.8	20.8	21.1	20.8	20.8	20.8
Ac	—	—	—	—	—	170.6	—	170.9	170.7	—	—
Ac	—	—	—	—	—	20.6	—	22.4	21.3	—	—
MeO	—	—	—	—	—	—	—	—	—	—	51.6

C	13	16	17	19	20	21	22	23	24	25
1-10	—	15.4	15.8	—	—	—	—	—	—	—
2	—	71.7	71.1	—	—	—	—	—	—	—
3	64.6	36.5	36.5	64.1	63.7	173.6	173.1	64.1	173.3	176.8
4	32.7	27.1	26.8	26.4	30.1	27.5	31.2	23.9	29.0	31.2
5	27.8	33.2	33.3	33.3	32.6	25.2	35.5	32.7	30.8	35.5
6	26.1	72.6	72.2	132.8	140.2	117.7	139.5	58.4	58.0	139.5
7	23.5	71.4	71.4	117.5	128.3	132.3	128.1	56.3	56.2	128.1
8	30.1	30.2	30.2	25.2	120.1	31.9	120.2	24.7	24.6	120.2
9	32.4	31.0	31.0	27.5	121.9	32.3	122.0	27.1	27.2	122.0
1′	130.7	129.4	128.9	128.3	126.3	128.3	127.8	125.6	125.5	127.7
2′	146.6	146.4	146.3	146.1	144.0	146.1	144.0	146.7	146.4	146.4
3′	119.6	120.4	119.9	120.0	117.0	120.0	117.1	120.4	120.4	121.1
4′	119.6	120.2	119.7	120.0	117.9	120.0	117.9	120.4	120.4	120.9
5′	146.5	146.6	146.4	146.1	144.4	146.1	144.3	146.5	146.6	146.6
6′	130.9	128.3	127.5	128.5	127.8	128.2	126.4	126.4	126.3	127.0
Ac	169.2	169.1	169.0	169.2	169.4	169.2	169.3	169.9	166.7	169.0
Ac	20.8	20.6	20.7	20.8	21.0	20.8	21.0	20.9	20.7	20.6
Ac	169.2	169.1	169.1	169.2	169.4	169.2	169.4	168.9	166.7	169.0
Ac	20.8	20.6	20.9	20.9	21.0	20.8	21.0	20.9	20.8	20.6
Ac	171.1	—	170.6	171.1	171.1	—	—	171.0	—	—
Ac	21.0	—	21.3	21.0	22.0	—	—	20.8	—	—
MeO	—	—	—	—	—	51.7	51.7	—	51.8	—

1468, 1368, 1183, 1016, 907, 815; ^1H NMR (Table 1); ^{13}C NMR (Table 2).

Compound 3. Obtained by selectively catalytic hydrogenation of **1** (97%); mp 64–66 °C; IR cm^{-1} 3019, 2954, 2868, 1760, 1471, 1368, 1180, 1020, 901, 817; ^1H NMR (Table 1); ^{13}C NMR (Table 2).

Compound 4. Obtained by MCPBA epoxidation of **1** followed by catalytic hydrogenation (62% overall yield); oil; IR cm^{-1} 2921, 2845, 1763, 1403, 1371, 1191, 1017, 908; ^1H NMR (Table 1); ^{13}C NMR (Table 2).

Compound 5. Obtained by MCPBA epoxidation of **3** (46%); mp 84–85 °C; IR cm^{-1} 3074, 2953, 2868, 1762, 1472, 1369, 1184, 1021, 899, 732; ^1H NMR (Table 1); ^{13}C NMR (Table 2).

Compound 6. Obtained by LAH reduction of **4** followed by acetylation (49%); mp 81–82 °C; IR cm^{-1} 3419, 2934, 2834, 1761, 1468, 1370, 1185, 1018, 908, 814; ^1H NMR (Table 1); ^{13}C NMR (Table 2).

Compound 7. Obtained by LAH reduction of **5** (21%); mp 102–103 °C; IR cm^{-1} 3502, 2946, 2859, 1765, 1470, 1372, 1182, 1013, 903, 811; ^1H NMR (Table 1); ^{13}C NMR (Table 2).

Compound 8. Obtained by LAH reduction of **5** followed by acetylation (22%); mp 105–106 °C; IR cm^{-1} 2954, 2868, 1764, 1732, 1470, 1368, 1183, 1019, 906, 818; ^1H NMR (Table 1); ^{13}C NMR (Table 2).

Compound 9. Obtained by acid hydrolysis followed by acetylation of **5** (27%) mp 98–99 °C; IR cm^{-1} 3411, 2954, 2866, 1763, 1746, 1472, 1369, 1185, 1018, 890; ^1H NMR (Table 1); ^{13}C NMR (Table 2).

Compound 10. Obtained by acid hydrolysis followed by acetylation of **5** (51%); mp 124–125 °C; IR cm^{-1} 3411,

Table 3. Cytotoxicity of prenylhydroquinones against neoplastic cultured cells (IC_{50} values, μM)

Compound	P-388	A-549	HT-29	Mel-28
Avarol[a]	3.1	6.0	6.0	6.0
1[a]	1.5	3.6	3.6	3.6
2	0.3	1.5	1.5	1.5
3	0.3	1.5	1.5	1.5
4	2.9	14.5	14.5	14.5
5	1.4	7.2	7.2	7.2
6	3.0	3.7	14.9	3.7
7	2.9	14.3	14.3	14.3
8	2.6	6.4	6.4	6.4
9	3.1	.2	6.2	6.2
10	3.1	6.2	6.2	5.2
11	3.3	16.4	16.4	16.4
12	3.0	3.0	15.0	15.0
13	2.9	2.9	14.4	2.9
14[a]	1.4	7.3	7.3	7.3
15[a]	6.9	6.9	13.8	13.8
16	13.8	13.8	13.8	13.8
17	> 25.0	> 25.0	> 25.0	> 25.0
19	1.4	2.9	2.9	2.9
20	0.3	2.9	2.9	2.9
21	2.9	14.5	14.5	14.5
22	0.3	3.6	3.6	3.6
23	6.9	6.9	6.9	13.8
24	15.1	15.1	15.1	15.1
25	10.0	10.0	10.0	10.0

[a]Bioactive data are cited from the literature previously reported.[1,2]

2954, 2866, 1763, 1746, 1472, 1369, 1185, 1018, 890; ^{1}H NMR (Table 1); ^{13}C NMR (Table 2).

Compound 11. Obtained by degradative H_5IO_6 oxidation of **4** (62%); mp 126–128 °C; IR cm^{-1} 2943, 2856, 2780, 1758, 1720, 1469, 1371, 1186,1017, 900; ^{1}H NMR (Table 1); ^{13}C NMR (Table 2).

Compound 12. Obtained by PDC oxidation **11** followed by CH_2N_2 methylation (64%); mp 71–73 °C; IR cm^{-1} 2932, 2866, 1760, 1720, 1470, 1371, 1184, 1018, 907, 817; ^{1}H NMR (Table 1); ^{13}C NMR (Table 2).

Compound 13. Obtained by LAH reduction of **11** followed by acetylation (43%); mp 82–83 °C; IR cm^{-1} 3063, 2932, 2856, 1763, 1730, 1469, 1365, 1186, 1017, 907, 815, 733; ^{1}H NMR (Table 1); ^{13}C NMR (Table 2).

Compound 16. Obtained by acid hydrolysis of **15** (28%); mp 125–126 °C; IR cm^{-1} 3541, 2970, 2935, 1766, 1470, 1369, 1184, 1051, 895, 733; ^{1}H NMR (Table 1); ^{13}C NMR (Table 2).

Compound 17. Obtained by acid hydrolysis of **4** followed by acetylation (31%); mp 138–140 °C; IR cm^{-1} 3073, 2959, 2878, 1763, 1738, 1471, 1370, 1184, 1038, 914, 732; ^{1}H NMR (Table 1); ^{13}C NMR (Table 2).

Compound 19. Obtained by LAH reduction of **18** followed by acetylation (61%); mp 80–81 °C; IR cm^{-1} 3030, 2954, 2867, 1763, 1730, 1468, 1365, 1180, 1017902, 831; ^{1}H NMR (Table 1); ^{13}C NMR (Table 2).

Compound 20. Obtained by LAH reduction of **18** followed by acetylation (31%); oil; IR cm^{-1} 3074, 2943, 2856, 1769, 1736, 1470, 1365, 1190, 1049, 897, 826; ^{1}H NMR (Table 1); ^{13}C NMR (Table 2).

Compound 21. Obtained by PDC oxidation of **18** followed by CH_2N_2 methylation (55%); mp 103–104 °C; IR cm^{-1} 2997, 2954, 1758, 1730, 1474, 1371, 1180, 1022, 902, 821; ^{1}H NMR (Table 1); ^{13}C NMR (Table 2).

Compound 22. Obtained by PDC oxidation of **18** followed by CH_2N_2 methylation (25%); mp 73–74 °C; IR cm^{-1} 3063, 2954, 2845, 1769, 1730, 1436, 1365, 1186, 1054, 897, 826; ^{1}H NMR (Table 1); ^{13}C NMR (Table 2).

Compound 23. Obtained by MCPBA epoxidation of **19** (73%); mp 74–75 °C ; IR cm^{-1} 3030, 2939, 2866, 1762, 1737, 1473, 1370, 1240, 1184, 1018, 899, 822; ^{1}H NMR (Table 1); ^{13}C NMR (Table 2).

Compound 24. Obtained by MCPBA epoxidation of **21** (82%); mp 119–121 °C; IR cm^{-1} 3073, 2953, 2856, 1763, 1734, 1472, 1370, 1183, 1024, 897; ^{1}H NMR (Table 1); ^{13}C NMR (Table 2).

Compound 25. Obtained by H_5IO_6 treatment of **24** (89%); mp 181–182 °C; IR cm^{-1} 3030, 2939, 1764, 1474, 1371, 1185, 1043, 911, 731; ^{1}H NMR (Table 1); ^{13}C NMR (Table 2).

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References

1. Gordaliza, M.; Miguel del Corral, J. M.; Castro, M. A.; Mahiques, M. M.; García-Grávalos, M. D.; San Feliciano, A. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 1859.
2. Miguel del Corral, J. M.; Gordaliza, M.; Castro, M. A.; Mahiques, M. M.; San Feliciano, A.; García-Grávalos, M. D. *Bioorg. Med. Chem*. **1998**, *6*, 31.
3. Minale, L.; Riccio, R.; Sodano, G. *Tetrahedron Lett*. **1974**, *15*, 3401.
4. De Rosa, S.; Minale, L.; Riccio, R.; Sodano, G. *J. Chem. Soc. Perkin Trans. 1* **1976**, 1408.
5. Minale, L. In *Marine Natural Products: Chemical and Biological Perspectives*; Scheuer, P. J., Ed.; Academic: New York, 1978; Vol. 1, Chapter 4.
6. Muller, W. E. G.; Maidhof, A.; Zahn, R. K.; Schröder, H. C.; Gasic, M. J.; Heidemann, D.; Bernd, A.; Kurelec, B.; Eich, E.; Seibert, G. *Cancer Res*. **1985**, *45*, 4822.
7. Sarin, P. S.; Sun, D.; Thornton, A.; Muller, W. E. G. *J. Nat. Cancer Inst*. **1978**, *78*, 663.
8. Bergeron, R. J.; Cavaragh, P. F., Jr.; Kline, S. J.; Hughes, R. G.; Elliot, G. T.; Porter, C. W. *Bioch. Bioph. Res. Commun*. **1984**, *121*, 848.
9. Corey, E. J.; Schmidt, G. *Tetrahedron Lett*. **1979**, *5*, 399.