New Selective Cytotoxic Diterpenylquinones and Diterpenylhydroquinones

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A new series of diterpenylquinone/hydroquinones has been prepared by Diels−Alder cycloaddition between three labdanic diterpenoids (myrceocommunic acid, methyl myrceocommunate, and myrceocommunyl acetate) and *p*-benzoquinone or 1,4-naphthoquinone. Influences of the quinone/hydroquinone fragment and other structural features, such as the different functionalities in the terpenic core, are considered in relation to the cytotoxicity toward neoplastic cells and the selectivity of these diterpenylnaphthoquinones/hydroquinones and anthraquinones. Several compounds showed IC_{50} values under the micromolar level, and four of these derivatives were evaluated at the NCI screening panel. The results showed an important selectivity toward renal cancer lines, identifying these compounds as a very promising group of antineoplastics.

Introduction

A variety of compounds having a quinone or hydroquinone moiety attached to a terpene unit have been isolated from marine algae and sponges. These natural products of mixed biogenetic origin mainly bear a cyclic or acyclic sesquiterpene or diterpene unit attached to an aromatic or pseudoaromatic ring with a varying degree of oxidation and changes in the substitution pattern.[1] Several of these marine metabolites displayed interesting cytotoxic, antiinflammatory, antifungal, and anti-HIV activities.

An especially notable terpene-hydroquinone/quinone family is that headed by avarol (Figure 1) and its related quinone, avarone, isolated from the sponge *Dysidea avara*.[2] Early studies indicated modest antibiotic and antileukaemic activities,[3] and subsequent research reported significant antiviral activity against HIV-1[4] that resulted in some patent applications.[5] Unfortunately, in vivo antiviral activity has not been confirmed by later assays, and some researchers have questioned those initial reports of antiviral activity.[6] However, due to their potential antitumor and anti-HIV activities, several syntheses of avarol and avarone have been published,[7] and an important number of new natural[8] and semisynthetic[9] derivatives have also been described, together with their cytotoxicities against several types of tumoral cells. Other kinds of activity reported for these types of compound are antioxidant,[10] platelet antiaggregation,[11] and enzymatic inhibition including that of HIV-1 reverse transcriptase.[12]

The main structural modifications deal with different substitution on the benzoquinone/hydroquinone moiety,

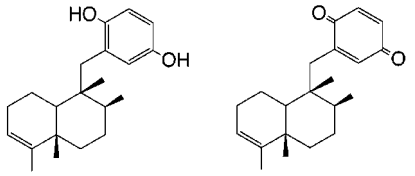

Figure 1. Chemical structures of avarol and avarone.

the terpenic part being mainly as found in the natural derivatives. In the past few years, our group initiated the study of the influence of the terpenyl and quinone sizes on the activity of this type of compound. With this aim, several monoterpenyl naphtho- and anthraquinones, with different functionalities in the side chain, were prepared and assayed.[13] From such earlier studies, it became clear that all the compounds prepared were more cytotoxic than 1,4-naphthoquinone itself and indeed showed potencies in the same range as avarol and avarone. This suggests that the sizes of both parts of the molecule, the terpene moiety and the quinone unit, were important for the cytotoxic activity.

Following this line of research, we now report the preparation of a new type of diterpenylquinone, from which we seek to determine whether the presence of a terpenic core larger than that of the natural products avarol and avarone could improve their bioactivity, and also to establish adequate structure−activity relationships.

Representative compounds were evaluated for their cytotoxicity against cultured cells of P-388 murine leukemia, A-549 human lung carcinoma, HT-29 human colon carcinoma, and MEL-28 human malignant melanoma. The IC_{50} values found ranged between 0.1 and 10 μM for naphthoquinone derivatives and between 2 and 21 μM for anthraquinone derivatives. These results have been compared with those for avarol and avarone (3−6 μM) which were taken as standards in our work.

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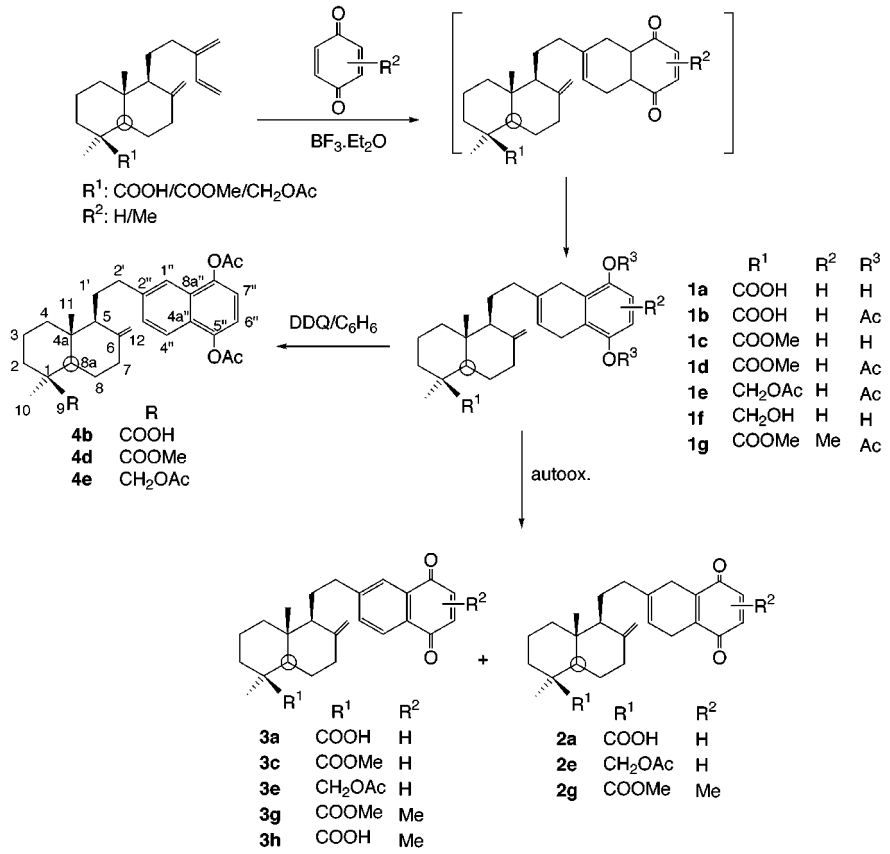
Scheme 1. Diels−Alder Cycloaddition between the Three Labdanic Derivatives and *p*-Benzoquinone



Chemistry

The diterpenylquinone/hydroquinone derivatives were prepared through a Diels−Alder cycloaddition between several natural diterpenoids as the diene and *p*-benzoquinone or 1,4-naphthoquinone as the dienophile component.

The natural labdanoid myrceocommunic acid, isolated from berries of *Juniperus oxycedrus*, was the starting material from which the other diterpenyl derivatives to be used as dienes were obtained. The acid was transformed into its methyl ester by treatment with an ethereal solution of diazomethane and into myrceocommunyl acetate by reduction with $LiAlH_4$ and further acetylation.[14]

Diels−Alder reaction between the three labdanic derivatives (myrceocommunic acid, methyl myrceocommunate, and myrceocommunyl acetate) and *p*-benzoquinone in the presence of $BF_3{\cdot}Et_2O$ (Scheme 1) yielded a reaction mixture from which, after column chromatography, the corresponding hydroquinones along with the autoxidation quinones were isolated. Thus the hydroquinone **1a** and the dihydronaphthoquinone **2a** were prepared from myrceocommunic acid. Compound **1a** was also transformed into **2a** by treatment with Ag_2O. Compound **1c** and **3c** were obtained from methyl myrceocommunate, and after acetylation of the reaction product of myrceocommunyl acetate and *p*-benzoquinone, **1e** and **2e** were isolated. Treatment of the acetylated hydroquinone **1e** with $LiAlH_4$ afforded the corresponding trihydroxy derivative **1f**. Derivatives **1g**, **2g**, and **3g** were obtained through the Diels−Alder condensation between methyl myrceocommunate and 2-methyl-*p*-benzoquinone. Naphthoquinone **3h** was obtained from myrceocommunic acid and 2-methyl-*p*-benzoquinone.

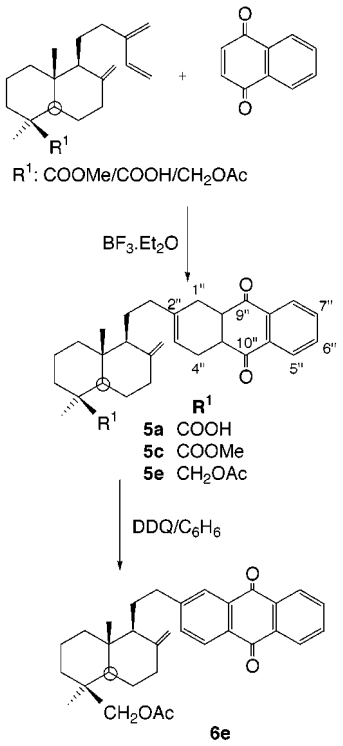
The formation of quinone derivatives and their degree of oxidation depended on the time of exposure to the air and on the time that the column chromatography lasted. It was verified that when the reaction product was adsorbed on silica gel for more than 1 day, the aromatic derivative **3** was essentially the only product recovered.

To avoid the autoxidation of the hydroquinone derivatives, in some cases, the reaction product was acetylated in order to fix the product as the dihydronaphthohydroquinone diacetate, before the chromatographic purification. Compounds **1b** and **1d** were obtained in this way. In some cases, the acetylated reaction products were used for further transformations without purification.

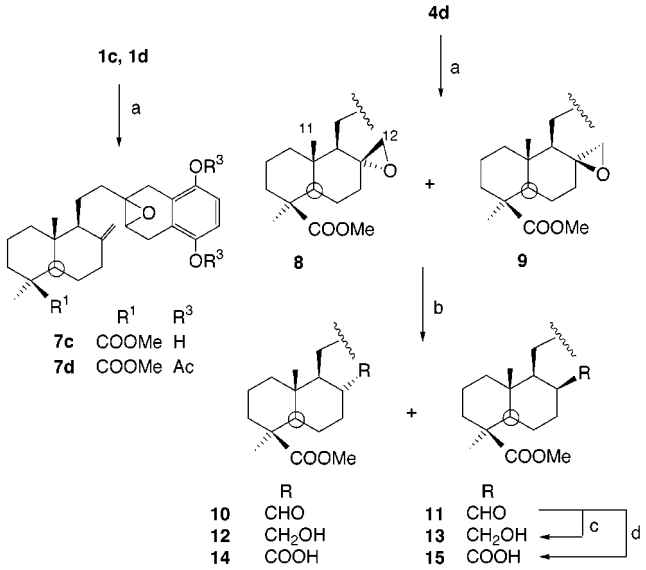
On the other hand, the maximum degree of unsaturation in the quinone fragment was achieved by treatment with DDQ or MnO_2. Thus from compounds **1b** and **1d** the corresponding naphthohydroquinone diacetates **4b** and **4d** were obtained with DDQ. In the DDQ oxidation of the reaction product between myrceocommunyl acetate and *p*-benzoquinone, quinone **3e** was also obtained together with the expected **4e**. The cyclocondensation product between myrceocommunic acid and *p*-benzoquinone yielded the naphthoquinone **3a** after oxidation with MnO_2.

To see the influence of the quinone core, the three starting labdadienes (methyl ester, acid, and acetate) were condensed with 1,4-naphthoquinone (Scheme 2) under the same conditions to get, after chromatography, the diketones **5a**, **5c**, and **5e**. The duplicity of several signals in both the ^1H and ^{13}C NMR spectra indicated a mixture of the two, *endo* and *exo*, Diels−Alder adducts. These ketones turned out to be stable and did not evolve

Scheme 2. Diels−Alder Cycloaddition between the Three Labdanic Derivatives and 1,4-Naphthoquinone



Scheme 3. Other Transformations Performed on the Terpenylnaphthohydroquinones[a]



[a] Reagents: (a) MCPBA, $NaHCO_3$, Cl_2CH_2; (b) $BF_3{\cdot}Et_2O$, C_6H_6; (c) $NaBH_4$, THF; (d) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH-H_2O.

spontaneously to the corresponding phenols or aromatized quinones. Only after treatment of **5e** with DDQ was the anthraquinone **6e** obtained.

With the aim of seeing the influence on the cytotoxic activity of different functionalities in the labdanic part of these molecules, further transformations, such as the epoxidation of the double bonds, were performed (Scheme 3). Thus, the selective epoxidation of the endocyclic double bond in the hydroquinonic derivatives **1c** and **1d** was done by treatment with 1 equiv of *m*-chloroperbenzoic acid (MCPBA) to afford **7c** and **7d**, respectively. It should be noted that the formation of the epoxide is preferred to the oxidation of the hydroquinonic system.

Other modifications were performed on **4d** (Scheme 3), which is one of the most potent compounds and also one of the more stable derivatives, having the naphthalene ring fully aromatized and the hydroxyl groups fixed as diacetates. The first modification was epoxidation of the most accessible part of the labdanic core, the $\Delta^{6(12)}$ double bond, which would allow further introduction of different functionalities. Thus, hydroquinone **4d** was treated with MCPBA to afford a mixture of the two possible epoxides **8** and **9**, which were separated by column chromatography. Treatment of the epoxides with $BF_3{\cdot}Et_2O$ yielded the aldehydes **10** and **11**, which were transformed into the alcohols **12** and **13** by reduction with $LiAlH_4$ and into the acids **14** and **15** by oxidation with $NaClO_2$ using 2-methyl-2-butene as scavenger. The stereochemistry of both epimers was determined by NOE experiments. When the methyl C-11 signal was irradiated, positive NOEs were observed in the signals of C-12 methylene protons in compounds **8**, **10**, and **12**.

Table 1. Cytotoxicity of Several Diterpenylquinones (Hydroquinones) against Neoplastic Cultured Cells (IC_{50} Values, μM)

compound	P-388	A-549	HT-29	MEL-28
avarol	3.2	6.4	6.4	6.4
avarol monoacetate	2.8	5.6	5.6	5.6
avarone	3.2	6.4	6.4	6.4
1b	2.5	2.5	10.1	5.0
1c	0.2	0.3	0.3	0.3
1d	0.2	0.2	0.2	0.2
1e	0.2	0.2	0.5	0.2
1f	0.6	1.2	1.2	1.2
2g	1.1	1.1	2.3	2.3
3c	0.1	0.2	0.2	0.2
3g	0.6	1.1	2.3	2.3
4b	0.2	0.2	0.2	0.2
4d	0.2	0.2	1.0	0.2
7c	0.9	1.9	2.3	1.9
7d	0.3	1.1	1.1	0.6
5c	2.1	2.1	10.6	5.3
5e	10.3	10.3	10.3	10.3
6e	>20.7	>20.7	>20.7	>20.7
8	0.05	0.23	0.23	0.4
9	0.1	0.5	0.5	0.5
10	0.05	0.2	0.2	0.2
11	0.05	0.2	0.2	0.2
12	2.0	2.0	2.0	2.0
13	2.0	2.0	2.0	2.0
14	1.8	1.8	1.8	1.8
15	1.8	1.8	1.8	1.8

Biological Results and Discussion

Most of the compounds being reported in this paper were evaluated for their bioactivity[15] against cultured cells of P-388 murine leukemia, A-549 human lung carcinoma, HT-29 human colon carcinoma, and MEL-28 malign human melanoma. The results obtained are shown in Table 1, and some effects were observed in relation to the influence of structures and substituents on the activity. avarol and related compounds were also included in the tests for comparison.

From the data shown in Table 1, some general observations can be made. Most of the naphthoquinone derivatives are more potent than avarol and avarone, and some of the compounds tested show a certain degree of selectivity toward leukemia P-388, as happens with

Table 2. LC_{50} (μM) Values in the Most Sensitive Cell Lines from the in Vitro NCI Screening for Derivatives **1d**, **3c**, **8**, and **11**

compd	tumor type	leukaemia	NSCL	colon	CNS	melanoma	ovarian	renal	prostate	breast	mean LC_{50}[d]
1d	*a*	HL-60(TB)	H-522	HCC-2998	SNB-75	SK-MEL-5	IGROV1	RXF-393	PC-3	BT-549	
1d	*b*	7.59	4.92	3.55	9.64	4.53	8.71	2.75	7.32	22.4	41.6
1d	*c*	17%	25%	57%	33%	87%	17%	100%	50%	0%	
3c	*a*	all	H-522	HCT-116	U-251	M14	IGROV1	ACHN	PC-3	BT-549	
3c	*b*	>100	6.55	42.8	32.9	9.87	36.3	6.29	32.7	20.7	20.9
3c	*c*	0%	43%	17%	33%	63%	50%	86%	50%	25%	
8	*a*	all	H-522	SW620	U251	SK-MEL-28	IGROV1	CAKI-1	PC-3	MDA-MB-435	
8	*b*	>100	2.28	2.16	1.78	0.70	2.89	0.66	4.14	1.71	28.6
8	*c*	0%	38%	71%	33%	75%	40%	100%	50%	63%	
11	*a*	all	HOP-62	KM12	SNB-75	SK-MEL-2	OVCAR-8	ACHN	PC-3	all	
11	*b*	>100	19.90	5.03	7.25	11.10	5.18	1.56	8.28	>100	5.98
11	*c*	0%	33%	17%	50%	25%	100%	57%	50%	0%	

[a] The most sensitive cell line within each panel. [b] LC_{50} (μM) for the most sensitive cell line. [c] Percentage of selectivity within each panel. [d] Arithmetic mean of the LC_{50} (μM) values for all cell lines tested.

the natural derivatives, e.g., 5 times more sensitive in the case of **9** with respect to the other lines, and 8 times in the case of **8** with respect to MEL-28.

Other observations and deductions can be made considering the labdanic and quinone parts separately.

(a) Regarding the modifications in the labdanic moiety, it seems useful to distinguish between modifications at position C-9 and in the double bond $\Delta^{6(12)}$.

• Changes in the degree of oxidation at C-9 yielded compounds with some differences in the cytotoxicity. Thus, the reduction of the methyl ester to the corresponding alcohol (**1c** vs **1f**) reduced the activity against all the cell lines tested, but the activity was partially recovered when its acetylated derivative is considered (**1f** vs **1e**).

• The presence of a free carboxylic acid group significantly reduced the potency (**1b** vs **1d**) in the case of compounds with a partially hydrogenated naphthalene ring, although in completely aromatized compounds, no significant changes in potency were observed (**4b** vs **4d**) except in the case of HT-29. Compound **1b**, which has a free carboxylic group at C-9, was the least potent compound of all the naphthalene derivatives tested, although it displayed a certain degree of selectivity against P-388 and A-549 cells.

• Modifications at the C-6 and C-12 positions of the decaline core yielded the most potent compounds of the series (**8**−**15**), especially when those positions contain reactive electrophilic functionalities such as epoxide or aldehyde. No differences in cytotoxicity were observed between the two epimers at C-6, except for the epoxides **8** and **9**, where the α disposition of the epoxide function may be slightly more potent than the corresponding β-epimer.

(b) Regarding the modifications in the quinone fragment:

• All the derivatives with an anthraquinone unit are much less potent than those having a naphthoquinone. Only compound **5c**, the one bearing the methyl ester on the labdanic part, retained values of IC_{50} in the same range as the naphthoquinones and then only in the case of the P-388 and A-549 systems.

• The substitution on the quinone/hydroquinone ring by a methyl group at positions 6″ or 7″ decreased the antineoplastic potency in all the cases and cell systems tested (**3g** vs **3c**).

• Epoxidation of the endocyclic double bond led to less potent compounds (**7d** vs **1d**).

• If the substituted quinonic ring is aromatized, a possible small improvement in the cytotoxicity is observed on P-388 (**3g** vs **2g**), and no differences were observed against the other cell lines tested.

• Aromatization of the hydroquinonic core (**4d** vs **1d**) and oxidation to the quinone (**4d** vs **3c**) did not modify significantly the potency except against HT-29 on which **4d** is 5 times less potent.

• Acetylation, initially performed to avoid autoxidation of hydroquinones before evaluation, did not modify the potency of these compounds (**1d** vs **1c**).

• While aromatization of the dihydronaphthohydroquinone improved the potency against P-388, in the case of anthraquinone derivatives an important decrease in the potency is observed.

Four of these terpenylnaphthoquinones (**1d**, **3c**, **8**, and **11**) were evaluated in the in vitro human disease-oriented tumor cell line screening panel developed at the NCI (Bethesda, MD). The panel includes about 60 diverse human tumor cell lines, grouped in nine different subpanels, representing diverse histologies, i.e., nonsmall cell lung, colon, central nervous system, renal, ovarian, prostate, and breast carcinomas, melanoma, and leukemia.

The compounds tested at the NCI showed similar antineoplastic fingerprints. For instance, if we consider the LC_{50} values (drug concentration required for killing 50% of the cells), all the leukemic lines were the least sensitive while all the renal cancer lines were effectively inhibited by the four compounds mentioned above. This is not in contradiction to our preliminary results (Table 1) because the assays we have done ourselves[15] differ from those performed at the NCI in the procedure and in the way of expressing the cytotoxic effect.[16] The IC_{50} values are similar, but not the same, to the GI_{50} values (drug concentration required for 50% growth inhibition) found by the NCI screening, in which the leukemia cell lines were more sensitive to the terpenylquinones tested (GI_{50} range: 1.65 to <0.01 μM).

In Table 2, the most sensitive cell line and its LC_{50} (μM) in the different nine subpanels of tumors are represented together with the relative cell line sensitivities (expressed as a percentage) within each panel. This selectivity is a measure of the specificity of action of a compound against the lines in a particular panel,

indicating whether a compound is sometimes, often, or always more effective against the lines in a particular panel than against the entire set of cell lines. Thus, a compound with a selectivity of 100% in a particular panel inhibited all of the cell lines in that panel better than the average inhibition against all cell lines in all panels. Similarly, a compound with a selectivity of 50% inhibited only half the cell lines in that panel better than the average over all cell lines. This average, expressed as the arithmetic mean of the LC_{50} values for all cell line responses measured for the given compound, is also included in Table 2.

It can be observed that compounds **1d**, **3c**, and **8** were also selective for several melanoma lines, and **11** showed significant selectivity against ovarian cell lines. When the COMPARE algorithm, a program that compares a complete set of cell sensitivities to those of standard agents or other agents present in the NCI database, was applied to compound **11**, all the correlation coefficients were <0.6 except for *N*,*N*-dibenzyldaunomycin (correlation coefficient $= 0.611$; correlation coefficients >0.6 can be considered significant). Daunomycin is known to intercalate into DNA and to inhibit topoisomerase II activity, and also, due to their quinone/hydroquinone character, the anthracycline analogues can express their biological activity via formation of free radicals. Those mechanisms could work for our compounds, although this should be confirmed.

Complementarily we tried to look for any structural similarity between avarol and our terpenylquinones using molecular modeling techniques. It seemed interesting to speculate on the possibility that these molecules would act at the same site as avarol, and in a similar molecular orientation. The introduction of an additional ring to the quinone system and the change of stereochemistry at the junction of the side chain with the terpene core (C-5) make it impossible to superimpose all atoms in any energetically accessible conformation of the two molecules. We have, however, been able to generate partial overlays by generating a diverse set of 100 conformations each of the epoxide **8** and the olefin **4d** and, using the program SQ,[17] to generate candidate superimpositions of these compounds on the X-ray crystal structure of avarol[18] (Figure 2). Initially we focused on the common structural features of **4d** and avarol, the double bond and the hydroquinone system to perform the overlay shown in Figure 2a.

However, the higher activity of the epoxide suggests that the double bond may not be a critical unit, and it is also reasonable to suppose that the hydroquinone moiety of avarol may not be in the ideal position relative to the terpene part of the molecule. The corresponding overlay (Figure 2b) shows one reasonable alignment of a low-energy conformer of the epoxide with avarol. Here, the hydroquinone moieties are not perfectly overlaid, although it would be quite possible for the oxygen atoms of both to interact with the same pair of hydrogen bond donor sites and for the hydroquinone aromatic rings to form similar stacking interactions with appropriate flat groups, on the biological target.

Further work is clearly needed to establish whether these molecules do indeed interact at the same site and whether the structure−activity relationships learned in the work presented here can be applied to other analogues of avarol and vice versa.

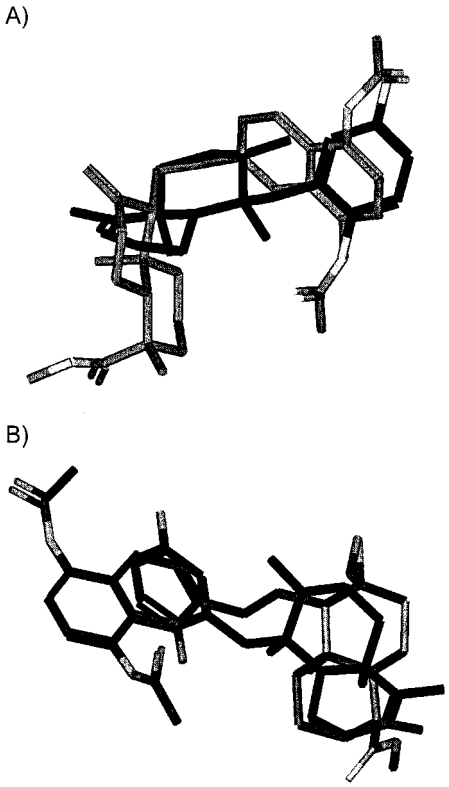


Figure 2. Superimposition of avarol and compounds **4d** and **8**. (A) Best overlay found by SQ for avarol (in black) with derivative **4d** in which the double bond moiety was constrained to coincide. (B) Best overlay found by SQ for avarol (in black) with epoxide **8**.

In summary, we have prepared a new series of diterpenylquinones with varied and potentially interesting activities and selectivities. Their construction from two independent parts with the option of further modification opens the possibility of a combinatorial exploration of such molecules. It is to be hoped that such an exploration would enable us to overcome some problems as may remain in converting these interesting leads into in vivo active compounds.

Experimental Section

Melting points were determined by heating in an external silicone bath and were uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter in $CHCl_3$ and UV spectra on a Hitachi 100−60 spectrophotometer in ethanol solution. IR spectra were obtained on a Beckmann (Acculab VIII) spectrophotometer in chloroform solution. GSMS spectra were measured on a Hewlett-Packard 5890 series II gas chromatograph (5971 series mass selective detector), and EIMS were run in a VG-MICROMASS ZAB-2F spectrometer working at 70 eV. HRMS were run in a VG TS-250 spectrometer working at 70 eV. NMR spectra were recorded at 200 MHz for ^1H and 50.3 for ^{13}C in deuterochloroform using TMS as internal reference, on a Bruker WP 200 SY. Chemical shift values are expressed in ppm followed by *multiplicity* and coupling constants (*J*) in hertz. Column chromatography (CC) was performed on silica gel (Merck no. 9385). TLC were carried out on silica gel 60 F_{245} (Merck, 0.25 mm thick). Solvents and reagents were purified by standard procedures as necessary. Elemental analyses were obtained with a LECO CHNS-932.

Chemistry. Starting Materials. Myrceocommunic acid was isolated from berries of *Juniperus oxycedrus* and trans-

formed into methyl myrceocommunate and myrceocommunyl acetate by described procedures.[14]

(1*S*,4a*R*,5*S*,8a*R*)-5-[2′-(5″,8″-Dihydroxy-1″,4″-dihydronaphthalen-2″-yl)-ethyl]-1,4a-dimethyl-6-methylene-decahydronaphthalene-1-carboxylic Acid (1a) and (1*S*,4a*R*,5*S*,8a*R*)-1,4a-Dimethyl-5-[2′-(5″,8″-Dioxo-1″,4″,5″,8″-tetrahydron-2″-yl)-ethyl]-6-methylene-decahydronaphthalene-1-carboxylic Acid (2a). General Procedure for the Diels−Alder Cycloaddition. To a solution of *p*-benzoquinone (178 mg, 1.65 mmol) in dry ether, myrceocommunic acid (500 mg, 1.65 mmol) and $BF_3{\cdot}Et_2O$ cat. were added. The mixture was kept stirring at room temperature under argon atmosphere for 24 h, then it was diluted with ether, washed with water, dried over Na_2SO_4, and the solvent evaporated off. The reaction product was chromatographed on silica gel to yield the following:

(a) 95 mg (19%) of unreacted myrceocommunic acid (Hex/EtOAc 95:5).

(b) 75 mg (11%) of **2a** (Hex/EtOAc 8:2). $[\alpha]^{22}_D$ +31.4° (*c*, 0.92). UV λ_{max} (ϵ): 246(21100), 283(3100). IR cm^{-1}: 3300, 1690, 1675, 1470. ^{1}H NMR ($CDCl_3$) δ: 0.59 (*s*, 3H, H-11), 1.23 (*s*, 3H, H-10), 0.90−2.00 (*m*, 14H, H-2, 3, 4, 5, 7, 8, 8a, 1′, 2′), 2.20 (*m*, 1H, H-7), 2.43 (*m*, 1H, H-4), 3.00 (*m*, 4H, H-4″, H-1″), 4.53 (*bs*, 1H, H-12a), 4.87(*bs*, 1H, H-12b), 5.49 (*bs*, 1H, H-3″), 6.73 (*s*, 2H, H-7″and H-6″). ^{13}C NMR ($CDCl_3$) δ: 12.9(C-11), 20.9(C-3), 21.8(C-1′), 24.9(C-4″), 26.1(C-8), 27.0(C-1″), 29.0(C-10), 36.0(C-2′), 38.0(C-2), 38.8(C-7), 39.3(C-4), 40.5(C-4a), 44.3(C-1), 55.8(C-5), 56.5(C-8a), 106.6(C-12), 116.3(C-3″), 134.6(C-2″), 136.3(C-7″ and C-6″), 139.6(C-4a″), 139.8(C-8a″), 147.9(C-6), 183.4(C-9), 186.9(C-8″ and C-5″). Anal. ($C_{26}H_{32}O_4$) C, H.

(c) 475 mg (70%) of **1a** (Hex/EtOAc 6:4). mp 106−108 °C (Hex−EtOAc). $[\alpha]^{22}_D$ +37.1° (*c*, 0.95). UV λ_{max} (ϵ): 290(10800). IR cm^{-1}: 3400, 1740, 1600, 1490. ^{1}H NMR ($CDCl_3$) δ: 0.61 (*s*, 3H, H-11), 1.15 (*s*, 3H, H-10), 0.90−2.40 (*m*, 16H, H-2, 3, 4, 5, 7, 8, 8a, 1′, 2′), 3.20 (*m*, 4H, H-4″,H-1″), 4.57 (*bs*, 1H, H-12a), 4.85 (*bs*, 1H, H-12b), 5.55 (*bs*, 1H, H-3″), 6.47 (*s*, 2H, H-7″ and H-6″). ^{13}C NMR ($CDCl_3$) δ: 13.6(C-11), 21.2(C-3), 23.2(C-1′), 26.4(C-4″), 27.6(C-8), 28.8(C-1″), 29.7(C-10), 37.6(C-2′), 39.3-(C-2), 40.0(C-7), 40.5(C-4), 41.5(C-4a), 45.2(C-1), 57.0(C-5), 57.5(C-8a), 107.1(C-12), 113.2(C-7″ and C-6″), 116.8(C-3″), 123.8(C-4a″), 124.1(C-8a″), 136.4(C-2″), 148.4(C-8″ and C-5″), 149.7(C-6), 181.5(C-9).

Treatment of **1a** (112 mg, 0.33 mmol) with Ag_2O (193 mg) in dry ether, at room temperature for 24 h, afforded after filtration and CC (Hex/EtOAc 8:2), 90 mg (67%) of **2a**.

(1*S*,4a*R*,5*S*,8a*R*)-5-[2′-(5″,8″-Diacetoxy-1″,4″-dihydronaphthalen-2″-yl)-ethyl]-1,4a-dimethyl-6-methylene-decahydronaphthalene-1-carboxylic Acid (1b). Acetylation of **1a** with acetic anhydride and pyridine yielded the diacetate **1b** (80%). $[\alpha]^{22}_D$ +40.7° (*c*, 1.01). UV λ_{max} (ϵ): 260-(7200). IR cm^{-1}: 1740, 1690, 1650, 1490. ^{1}H NMR ($CDCl_3$) δ: 0.62 (*s*, 3H, H-11), 1.23 (*s*, 3H, H-10), 0.90−2.50 (*m*, 16H, H-2, 3, 4, 5, 7, 8, 8a, 1′, 2′), 2.31 (*s*, 3H, OAc), 2.32 (*s*, 3H, OAc), 3.10 (*m*, 2H, H-1″), 3.20 (*bs*, 2H, H-4″), 4.54 (*bs*, 1H, H-12a), 4.88 (*bs*, 1H, H-12b), 5.53 (*bs*, 1H, H-3″), 6.93 (*s*, 2H, H-7″and H-6″).^{13}C NMR ($CDCl_3$) δ: 12.9 (C-11), 20.0 (C-3), 20.8 (2 × $OCOCH_3$), 21.5 (C-1′), 25.2(C-4″), 26.2(C-8), 27.7(C-1″), 29.0-(C-10), 35.7(C-2′), 37.9(C-2), 38.8(C-7), 39.1(C-4), 40.5(C-4a), 44.3(C-1), 55.3(C-5), 56.3(C-8a), 106.5(C-12), 116.7(C-3″), 119.9-(C-7″ and C-6″), 128.6(C-4a″), 128.9(C-8a″), 134.3(C-2″), 146.2-(C-8″ and C-5″), 148.1(C-6), 169.3(2 × $OCOCH_3$), 184.0(C-9). Anal. ($C_{30}H_{38}O_6$) C, H. HRMS (FAB-POSI, M + 1) calcd 495.2746, found 495.2673.

(1*S*,4a*R*,5*S*,8a*R*)-5-[2′-(5″,8″-Dioxo-5″,8″-dihydro-naphthalen-2″-yl)-ethyl]-1,4a-dimethyl-6-methylene-decahydronaphthalene-1-carboxylic Acid (3a). The cycloaddition product between myrceocommunic acid (490 mg, 1.62 mmol) and *p*-benzoquinone was treated with MnO_2 (1.2 g) under refluxed benzene (15 mL) for 3 h. Then the mixture was filtered, the solid washed with EtOAc, and the organic solvent evaporated off. The residue was chromatographed (Hex/EtOAc 7:3) to yield **3a** (260 mg, 40%). ^{1}H NMR ($CDCl_3$) δ: 0.57 (*s*, 3H, H-11), 1.19 (*s*, 3H, H-10), 0.90−2.00 (*m*, 12H, H-2, 3, 4, 5, 7, 8, 8a, 1′), 2.10 (*m*, 1H, H-7), 2.50 (*m*, 2H, H-2′, H-4), 2.90 (*m*, 1H, H-2′), 4.61(*s*, 1H, H-12a), 4.93(*s*, 1H, H-12b), 6.93 (*s*, 2H, H-7″and H-6″), 7.51 (*dd*, 1H, J_1 = 8.0, J_2 = 1.5, H-3″), 7.83 (*d*, 1H, J = 1.5, H-1″), 7.96 (*d*, 1H, J = 8.0, H-4″). ^{13}C NMR ($CDCl_3$) δ: 12.7(C-11), 19.8(C-3), 25.4(C-1′), 25.9(C-8), 28.9(C-10), 34.9(C-2′), 37.7(C-2), 38.6(C-7), 39.0(C-4), 40.4(C-4a), 44.0(C-1), 55.3(C-8a), 56.1(C-5), 106.8(C-12), 126.0(C-1″), 126.6(C-4″), 129.8(C-4a″), 131.8(C-8a″), 134.0(C-3″), 138.5(C-6″), 138.7(C-7″), 147.5(C-2″), 150.2(C-6), 184.0(C-9), 184.9(C-5″), 185.4(C-8″). Anal. ($C_{26}H_{30}O_4$) C, H.

(1*S*,4a*R*,5*S*,8a*R*)-1,4a-Dimethyl-5-[2′-(6″(7″)-methyl-5″,8″-dioxo-5″,8″-dihydronaphtha″-yl)-ethyl]-6-methylene-decahydronaphthalene-1-carboxylic Acid (3h). From the reaction product between myrceocommunic acid (120 mg, 0.40 mmol) and 2-methyl-*p*-benzoquinone (49 mg, 0.40 mmol), according to the procedure described above and after 48 h of exposure of the reaction product to the air, 70 mg (42%) of **3h** were isolated (Hex/EtOAc 6:4). UV λ_{max} (ϵ): 260(19000), 319-(2000). IR cm^{-1}: 3400, 1700, 1675, 1600, 1450, 1270. ^{1}H NMR ($CDCl_3$) δ: 0.59 (*s*, 3H, H-11), 1.22 (*s*, 3H, H-10), 0.90−2.00 (*m*, 12H, H-2, 3, 4, 5, 7, 8, 8a, 1′), 2.15 (*m*, 1H, H-7), 2.18 (*s*, 3H, 6″/7″-CH_3), 2.45 (*m*, 1H, H-4), 2.55 (*m*, 1H, H-2′), 2.90 (*m*, 1H, H-2′), 4.63 (*s*, 1H, H-12a), 4.95 (*s*, 1H, H-12b), 6.77(*s*, 1H, H-6″/7″), 7.52 (*dd*, 1H, J_1 = 8.0, J_2 = 1.9, H-3″), 7.87 (*d*, 1H, J = 1.9, H-1″), 8.00 (*d*, 1H, J = 8.0, H-4″). ^{13}C NMR ($CDCl_3$) δ: 12.8(CH_3), 19.9(CH_2), 18.4(CH_3), 25.5(CH_2), 26.1(CH_2), 29.0-(CH_3), 35.0(CH_2), 38.0(CH_2), 38.7(CH_2), 39.2(CH_2), 40.6(C), 44.3(C), 55.5(CH), 56.4(CH), 106.8(CH_2), 126.4(CH), 126.9(CH), 130.3 (C), 132.6 (C), 133.7(CH), 135.8(CH), 147.6(C), 147.8 (C), 149.9(C), 183.5(*C*OOH), 185.0(*C*O), 186.2(*C*O).

(1*S*,4a*R*,5*S*,8a*R*)-5-[2′-(9″,10″-Dioxo-1″,4″,4a″,9″,9a″,10″-hexahydrthyl]-1,4a-dimethyl-6-methylene-decahydronaphthalene-1-carboxylic Acid (5a). Diels−Alder reaction between myrceocommunic acid (46 mg, 0.16 mmol) and 1,4-naphthoquinone (25 mg, 0.16 mmol) afforded, after column chromatography (CC) of the reaction product (Hex/EtOAc 8:2), 52 mg (70%) of **5a**. $[\alpha]^{22}_D$ +20.7° (*c*, 0.86). UV λ_{max} (ϵ): 220-(13200), 250(13000). IR cm^{-1}: 3400, 1690, 1600, 1470, 1210. ^{1}H NMR ($CDCl_3$) δ: 0.55 (*s*, 3H, H-11), 1.25 (*s*, 3H, H-10), 0.90−2.50 (*m*, 16H, H-2, 3, 4, 5, 7, 8, 8a, 1′, 2′), 3.40 (*m*, 6H, H-4″, 1″, 9a″, 4a″), 4.49 (*s*, 1H, H-12a), 4.83 (*s*, 1H, H-12b), 5.41 (*bs*, 1H, H-3″), 7.75 (*m*, 2H, H-7″and 6″), 8.05 (*m*, 2H, H-8″ and H-5″). ^{13}C NMR ($CDCl_3$) δ: 12.9(CH_3), 20.0(CH_2), 21.6(CH_2), 24.6(CH_2), 26.2(CH_2), 27.8(CH_2), 29.0(CH_3), 36.3-(CH_2), 38.1(CH_2), 38.8(CH_2), 39.1(CH_2), 40.5(C), 44.3(C), 46.6-(CH), 47.4(CH), 55.1(CH), 56.5(CH), 106.4(CH_2), 118.7(CH), 126.9(2 × C), 134.2(C and 2 × CH), 135.9(C), 136.2(C), 148.0-(C), 182.8(*C*OOH), 187.9(*C*O), 188.1(*C*O).

(1*S*,4a*R*,5*S*,8a*R*)-5-[2′-(5″,8″-Dihydroxy-1″,4″-dihydronaphthalen-2″-yl)-ethyl]-1,4a-dimethyl-6-methylene-decahydronaphthalene-1-carboxylic Acid Methyl Ester (1c) and (1*S*,4a*R*,5*S*,8a*R*)-5-[2′-(5″,8″-Dioxo-5″,8″-dihydronaphthalen-2″-yl)-ethyl]-1,4a-dimethyl-6-methylene-decahydronaphthalene-1-carboxylic Acid Methyl Ester (3c). Cycloaddition between methyl myrceocommunate (1.7 g, 3.69 mmol) and *p*-benzoquinone (398 mg, 3.69 mmol) yielded, after CC of the reaction product, the following compounds:

(a) 195 mg (11%) of unreacted methyl myrceocommunate (Hex/EtOAc 95:5).

(b) 227 mg (15%) of **3c** (Hex/EtOAc 9:1). $[\alpha]^{22}_D$ +31.7° (*c*, 1.53). UV λ_{max} (ϵ): 245(17000), 330(25000). IR cm^{-1}: 1735, 1675, 1625, 1470. EIMS *m*/*z*: 420(M^+). ^{1}H NMR ($CDCl_3$) δ: 0.50 (*s*, 3H, H-11), 1.17 (*s*, 3H, H-10), 0.90−2.00 (*m*, 12H, H-2, 3, 4, 5, 7, 8, 8a, 1′), 2.15 (*m*, 1H, H-7), 2.45 (*m*, 1H, H-4), 2.55 (*m*, 1H, H-2′), 2.90 (*m*, 1H, H-2′), 3.60 (*s*, 3H, OCH_3), 4.63 (*bs*, 1H, H-12a), 4.95(*bs*, 1H, H-12b), 6.94 (*s*, 2H, H-7″ and H-6″), 7.54 (*dd*, 1H, J_1 = 7.9, J_2 = 1.8, H-3″), 7.87 (*d*, 1H, J = 1.8, H-1″), 8.00 (*d*, 1H, J = 7.9, H-4″). ^{13}C NMR ($CDCl_3$) δ: 13.0-(C-11), 20.3(C-3), 25.8(C-1′), 26.6(C-8), 29.2(C-10), 35.3(C-2′), 38.5(C-2), 39.1(C-7), 39.5(C-4), 40.7(C-4a), 44.7(C-1), 51.5-(OCH_3), 55.8(C-5), 56.6(C-8a), 107.1(C-12), 126.4(C-1″), 127.1-(C-4″), 130.3(C-8a″ and C-4a″), 134.4(C-3″), 138.9(C-6″), 139.1-(C-7″), 148.0(C-6), 150.7(C-2″), 178.0(C-9), 185.3(C-5″), 185.8(C-8″). Anal. ($C_{27}H_{32}O_4$) C, H.

(c) 771 mg (49%) of **1c** (Hex/EtOAc 7:3). mp 97−99 °C (Hex−AcOEt). $[\alpha]^{22}_D$ +49.7° (*c*, 0.56). UV λ_{max} (ϵ): 290(5100). IR cm^{-1}: 3400, 1735, 1660, 1480. ^1H NMR ($CDCl_3$) δ: 0.47 (*s*, 3H, H-11), 1.26 (*s*, 3H, H-10), 0.95−2.00 (*m*, 14H, H-2, 3, 4, 5, 7, 8, 8a, 1′, 2′), 2.17 (*m*, 1H, H-7), 2.40 (*m*, 1H, H-4), 3.20 (*m*, 2H, H-1″), 3.28 (*bs*, 2H, H-4″), 3.60 (*s*, 3H, OCH_3), 4.55 (*bs*, 1H, H-12a), 4.85(*bs*, 1H, H-12b), 5.54 (*bs*, 1H, H-3″), 6.50(*s*, 2H, H-7″ and H-6″). ^{13}C NMR ($CDCl_3$) δ: 12.8(C-11), 20.1(C-3), 22.0(C-1′), 25.2(C-4″), 26.4(C-8), 27.6(C-1″), 28.7(C-10), 36.3-(C-2′), 38.3(C-2), 38.9(C-7), 39.3(C-4), 40.4(C-4a), 44.6(C-1), 51.3(OCH_3), 55.7(C-5), 56.5(C-8a), 106.6(C-12), 112.5(C-7″ and C-6″)117.3(C-3″), 122.6(C-4a″), 123.0(C-8a″), 135.0(C-2″) 147.0-(C-8″ and C-5″), 148.1(C-6), 178.4(C-9). HRMS (FAB-POSI, M + 1) calcd 425.2691, found 425.2652.

(1*S*,4a*R*,5*S*,8a*R*)-5-[2′-(5″,8″-Diacetoxy-1″,4″-dihydronaphthalen-2″-yl)-ethyl]-1,4a-dimethyl-6-methylene-decahydronaphthalene-1-carboxylic Acid Methyl Ester (1d). Acetylation of **1c** with acetic anhydride and pyridine yielded the diacetate **1d** (70%). $[\alpha]^{22}_D$ +34.9° (*c*, 1.03). UV λ_{max} (ϵ): 265(6400). IR cm^{-1}: 1775, 1725, 1650, 1475. GCMS (220−290 °C, 5 °C/min, HP-1 column), >99%, t_R = 23.19 min, (*m*/*z*) 508 (M^+). ^1H NMR ($CDCl_3$) δ: 0.52 (*s*, 3H, H-11), 1.17 (*s*, 3H, H-10), 1.00−2.00 (*m*, 14H, H-2, 3, 4, 5, 7, 8, 8a, 1′, 2′), 2.15 (*m*, 1H, H-7), 2.29 (*s*, 3H, OAc), 2.31 (*s*, 3H, OAc), 2.43 (*m*, 1H, H-4), 3.08 (*m*, 2H, H-1″), 3.18 (*bs*, 2H, H-4″), 3.60 (*s*, 3H, OCH_3), 4.53 (*bs*, 1H,H-12a), 4.87 (*bs*, 1H,H-12b), 5.52 (*bs*, 1H,H-3″), 6.91 (*s*, 2H,H-7″ and H-6″). ^{13}C NMR ($CDCl_3$) δ: 13.0(C-11), 20.3(C-3), 20.3 (2 × OCO*C*H_3), 21.7(C-1′), 25.3(C-4″), 26.3(C-8), 28.0(C-1″), 29.1(C-10), 36.1(C-2′), 38.6(C-2), 39.2-(C-7), 39.5(C-4), 40.6(C-4a), 44.7(C-1), 51.5(OCH_3), 55.6(C-5), 56.6(C-8a), 106.7(C-12), 117.0(C-3″), 120.3 (C-7″ and C-6″), 128.8(C-4a″), 128.9(C-8a″), 134.6(C-2″), 146.5 (C-8″ and C-5″), 148.5(C-6), 169.9(2 × *O*C*O*CH_3), 178.2(C-9). Anal. ($C_{31}H_{40}O_6$) C, H. HRMS (FAB-POSI, M + 1) calcd 509.2903, found 509.2887.

(1*S*,4a*R*,5*S*,8a*R*)-5-[2′-(5″,8″-Diacetoxy-6″(7″)-methyl-1″,4″-dihydronaphthalen-2′yl]-1,4a-dimethyl-6-methylene-decahydronaphthalene-1-carboxylic Acid Methyl Ester (1g), (1*S*,4a*R*,5*S*,8a*R*)-1,4a-Dimethyl-5-[2′-(6″(7″)-methyl-5″,8″-dioxo-1″,4″,5″,8′naphthalen-2″-yl)-ethyl]-6-methylene-decahydronaphthalene-1-carboxylic Acid Methyl Ester (2g), and (1*S*,4a*R*,5*S*,8a*R*)-1,4a-Dimethyl-5-[2′-(6″-(7″)-methyl-5″,8″-dioxo-5″,8″-dihydro-naphth2″-yl)-ethyl]-6-methylene-decahydronaphthalene-1-carboxylic Acid Methyl Ester (3g). From the reaction between methyl myrceocommunate (2.25 g, 7.11 mmol) and 2-methyl-*p*-benzoquinone (675 mg, 7.11 mmol) were obtained the following compounds after acetylation and CC of the reaction product:

(a) 534 mg (24%) of unreacted methyl myrceocommunate (Hex/EtOAc 95:5).

(b) 340 mg (11%) of **3g** (Hex/EtOAc 9:1). UV λ_{max} (ϵ): 245-(18300), 260(19100). IR cm^{-1}: 1730, 1680, 1640, 1480. GCMS (220−290 °C, 5 °C/min, SPB-1 column), >99%, t_R = 21.56 min, (*m*/*z*) 434 (M^+). ^1H NMR ($CDCl_3$) δ: 0.49 (*s*, 3H, H-11), 1.16 (*s*, 3H, H-10), 0.90−2.00 (*m*, 12H, H-2, 3, 4, 5, 7, 8, 8a, 1′), 2.10 (*m*, 1H, H-7), 2.18 (*s*, 3H, 6″/7″-CH_3), 2.40 (*m*, 1H, H-4), 2.55 (*m*, 1H, H-2′), 2.90 (*m*, 1H, H-2′), 3.60 (*s*, 3H, OCH_3), 4.63 (*s*, 1H, H-12a), 4.95 (*bs*, 1H, H-12b), 6.61 (*bs*, 1H, H-7″), 7.51-(*dd*, 1H, J_1 = 7.9, J_2 = 1.8, H-3″), 7.87 (*d*, 1H, *J* = 1.8, H-1″), 8.00(*d*, 1H, *J* = 7.9, H-4″). ^{13}C NMR ($CDCl_3$) δ: 12.6(CH_3), 16.4(CH_3), 20.0(CH_2), 25.5(CH_2), 26.3(CH_2), 28.8(CH_3), 35.0-(CH_2), 38.3(CH_2), 38.8(CH_2), 39.2(CH_2), 40.4(C), 44.4(C), 51.2-(OCH_3), 55.5(CH), 56.4(CH), 106.7(CH_2), 126.4(CH), 126.9 (CH), 130.1 (C), 132.3 (C), 133.7(CH), 135.6(C), 135.8(CH), 147.7(C), 149.9 (C), 177.7(*C*OOCH$_3$), 185.4(2 × *C*O). Anal. ($C_{28}H_{34}O_4$) C, H. HRMS (FAB-POSI, M + 1) calcd 435.2535, found 435.2477.

(c) 820 mg (27%) of **2g** (Hex/EtOAc 9:1). UV λ_{max} (ϵ): 248-(17300), 285(1900). IR cm^{-1}: 1370, 1670, 1635, 1480. ^1H NMR ($CDCl_3$) δ: 0.49 (*s*, 3H, H-11), 1.16 (*s*, 3H, C-10), 0.95−2.50 (*m*, 16H, H-2, 3, 4, 5, 7, 8, 8a, 1′, 2′), 2.04 (*s*, 3H, 6″/7″-CH_3), 3.00 (*m*, 4H, H-4″, H-1″), 3.60 (*s*, 3H, OCH_3), 4.51 (*bs*, 1H, H-12a), 4.85(*bs*, 1H, H-12b), 5.46 (*bs*, 2H, H-3″), 6.55 (*s*,1H, H-7″). ^{13}C NMR ($CDCl_3$) δ: 12.6(CH_3), 15.7(CH_3), 20.0(CH_2), 25.0(CH_2), 25.4(CH_2), 26.3(CH_2), 27.1(CH_2), 28.8(CH_3), 35.9-(CH_2), 38.2(CH_2), 38.7(CH_2), 39.2(CH_2), 40.3(C), 44.3(C), 55.1-(OCH_3), 55.6(CH), 56.3(CH), 106.5(CH_2), 116.4(CH), 133.0(CH), 134.4(C), 134.5(C), 139.4(2 × C),145.4 (C), 147.8(C), 177.7-(*C*OOCH$_3$), 187.1(*C*O), 187.4(*C*O). Anal. ($C_{28}H_{36}O_4$) C, H. HRMS (FAB-POSI, M + 1) calcd 437.2691, found 437.2683.

(d) 1.15 g (31%) of **1g** (Hex/EtOAc 8:2). UV λ_{max} (ϵ): 294-(5600). IR cm^{-1}: 1770, 1720, 1610, 1470. GCMS (220−290 °C, 5 °C/min, SPB-1 column), >99%, t_R = 27.49 min, (*m*/*z*) 522 (M^+). ^1H NMR ($CDCl_3$) δ: 0.52 (*s*, 3H, H-11), 1.18 (*s*, 3H, H-10), 0.95−2.50 (*m*, 16H, H-2, 3, 4, 5, 7, 8, 8a, 1′, 2′), 2.12(*s*, 3H, 6″/7″-CH_3), 2.30 (*s*, 3H, OAc), 2.34 (*s*, 3H, OAc), 3.05 (*m*, 2H, H-1″), 3.20 (*bs*, 2H, H-4″), 3.61 (*s*, 3H, OCH_3), 4.53 (*bs*, 1H, H-12a), 4.87(*bs*, 1H, H-12b), 5.51 (*bs*, 1H, H-3″), 6.60 (*s*, 1H, H-6″/7″). ^{13}C NMR ($CDCl_3$) δ: 12.8(CH_3), 18.4(CH_3), 20.1(CH_2), 20.5(2 × OCO*C*H_3), 21.5(CH_2), 25.3(CH_2), 26.4(CH_2), 27.8(CH_2), 28.9(CH_3), 35.8(CH_2), 38.3(CH_2), 38.8(CH_2), 39.2(CH_2), 40.3-(C), 44.4(C), 51.1(OCH_3), 55.3(CH), 56.3(CH), 106.4(CH_2), 116.8(CH), 121.4(C), 125.8(C), 128.7(C), 134.3(C), 145.0(C), 146.0(C), 148.2(2 × C), 168.7(*O*C*O*CH$_3$), 169.3(*O*C*O*CH$_3$), 177.8(*C*OOCH$_3$).

(1*S*,4a*R*,5*S*,8a*R*)-5-[2′-(9″,10″-Dioxo-1″,4″,4a″,9″,9a″,10″-hexahydrhyl]-1,4a-dimethyl-6-methylene-decahydronaphthalene-1-carboxylic Acid Methyl Ester (5c). From the reaction product between methyl myrceocommunate (324 mg, 1.02 mmol) and 1,4-naphthoquinone (162 mg, 1.02 mmol) was obtained 302 mg (80%) of **5c** after CC (Hex/EtOAc 8:2). $[\alpha]^{22}_D$ +14.7° (*c*, 2.02). UV λ_{max} (ϵ): 222(14700), 252(13400). IR cm^{-1}: 1740, 1710, 1690, 1260. ^1H NMR ($CDCl_3$) δ: 0.44 (*s*, 3H, H-11), 1.14 (*s*, 3H, H-10), 0.90−2.50 (*m*, 16H, H-2, 3, 4, 5, 7, 8, 8a, 1′, 2′), 3.40 (*m*, 6H, H-4″, 1″, 9a″, 4a″), 3.56 (*s*, 3H, OCH_3), 4.43 (*bs*, 1H, H-12a), 4.77 (*bs*, 1H, H-12b), 5.36 (*bs*, 1H, H-3″), 7.71 (*m*, 2H, H-7″ and 6″), 8.01 (*m*, 2H, H-8″and H-5″). ^{13}C NMR ($CDCl_3$) δ: 12.6(CH_3), 20.0(CH_2), 21.4(CH_2), 24.6(CH_2), 26.3(CH_2), 27.8(CH_2), 28.8(CH_3), 36.3(CH_2), 38.3-(CH_2), 38.8(CH_2), 39.3(CH_2), 40.3(C), 44.4(C), 46.5(CH), 47.2-(CH), 51.0(OCH_3), 55.5(CH), 56.3(CH), 106.3(CH_2), 118.1(CH), 126.8(2 × CH), 134.2(2 × CH), 135.8(C), 136.2(C), 148.0(C), 177.6(*C*OOCH$_3$), 187.8(*C*O), 188.1(*C*O). Anal. ($C_{31}H_{38}O_4$) C, H.

(1*S*,4a*R*,5*S*,8a*R*)-5-[2′-(5″,8″-Diacetoxy-1″,4″-dihydronaphthalen-2″-yl)-ethyl]-1,4a-dimethyl-6-methylene-decahydronaphthalen-1-ylmethyl Acetate (1e) and (1*S*,-4a*R*,5*S*,8a*R*)-5-[2′-(5″,8″-Dioxo -1″,4″,5″,8″-tetrahydronaphthalen-2″-yla-dimethyl-6-methylene-decahydro-naphthalen-1-ylmethyl Acetate (2e). Diels−Alder cycloaddition of myrceocommunyl acetate (276 mg, 0.84 mmol) with *p*-benzoquinone (90 mg, 0.84 mmol) yielded, after acetylation and CC of the reaction product, the following compounds:

(a) 50 mg (18%) of unreacted myrceocommunyl acetate (Hex/EtOAc 85:15).

(b) 110 mg (30%) of **2e** (Hex/EtOAc 8:2). $[\alpha]^{22}_D$ +16.8° (*c*, 1.57). UV λ_{max} (ϵ): 245(24000), 280(6000). IR cm^{-1}: 1750, 1675, 1660, 1475. ^1H NMR ($CDCl_3$) δ: 0.67 (*s*, 3H, H-11), 0.94 (*s*, 3H, H-10), 0.90−2.00 (*m*, 14H, H-2, 3, 4, 5, 7, 8, 8a, 1′, 2′), 2.20 (*m*, 1H, H-7), 2.40 (*m*, 1H, H-4), 3.00 (*m*, 4H, H-4″, H-1″), 3.83 (*d*, 1H, *J* = 11, H-9a), 4.20 (*d*, 1H, *J* = 11, H-9b), 4.52 (*bs*, 1H, H-12a), 4.84 (*bs*, 1H, H-12b), 5.47 (*bs*, 1H, H-3″), 6.72 (*s*, 2H, H-7″and H-6″). ^{13}C NMR ($CDCl_3$) δ: 15.3(C-11), 18.9-(C-3), 20.9(OCO*C*H_3), 21.6(C-1′), 24.6(C-8), 24.9(C-4″), 27.0-(C-1″), 27.6(C-10), 35.8(C-2′), 36.3(C-2), 37.4(C-4a), 38.6(C-7), 39.6(C-1), 39.9(C-4), 56.3(C-5), 56.5(C-8a), 66.8(C-9), 106.9(C-12), 116.3(C-3″), 134.6(C-2″), 136.3(C-7″ and C-6″), 139.6(C-8a″ and C-4a″), 147.7(C-6), 171.2(*O*C*O*CH$_3$), 187.1(C-8″ and C-5″).

(c) 90 mg (21%) of **1e** (Hex/EtOAc 7:3). $[\alpha]^{22}_D$ +24.6° (*c*, 1.44). UV λ_{max} (ϵ): 275(14000). IR cm^{-1}: 1770, 1740, 1600, 1470. ^1H NMR ($CDCl_3$) δ: 0.70 (*s*, 3H, H-11), 0.96 (*s*, 3H, H-10), 0.95−2.50 (*m*, 16H, H-2, 3, 4, 5, 7, 8, 8a, 1′, 2′), 2.03 (*s*, 3H, OAc), 2.31 (*s*, 3H, OAc), 2.32 (*s*, 3H, OAc), 3.09 (*m*, 2H, H-1″), 3.19 (*bs*, 2H, H-4″), 3.85 (*d*, 1H, *J* = 11.0, H-9a), 3.85 (*d*, 1H, *J* = 11.0, H-9b), 4.23 (*bs*, 1H, H-12a), 4.85 (*bs*, 1H, H-12b), 5.52 (*bs*, 1H, H-3″), 6.92 (*s*, 2H, H-7″ and H-6″). ^{13}C NMR ($CDCl_3$) δ: 15.9(C-11), 19.0(C-3), 20.8(3 × OCO*C*H_3), 21.4(C-1′), 24.6-(C-8), 25.2(C-4″), 27.6(C-10), 27.8(C-1″), 35.7(C-2′), 36.3(C-2),

37.4(C-4a), 38.6(C-7), 39.0(C-4), 39.6(C-1), 56.3(C-5, C-8a), 66.9(C-9), 106.8(C-12), 116.8(C-3″), 120.0(C-7″ and C-6″), 128.8(C-4a″), 128.9(C-8a″), 134.5(C-2″), 146.2(C-8″ and 5″), 148.0(C-6), 169.0(2 × $OCOCH_3$), 171.2($OCOCH_3$). Anal. ($C_{32}H_{42}O_6$) C, H. HRMS (FAB-POSI, M + 1) calcd 523.3059, found 523.3003.

(1*S*,4a*R*,5*S*,8a*R*)-5-[2′-(5″,8″-Dihydroxy-1″,4″-dihydronaphthalen-2″-yl)-ethyl]-1,4a-dimethyl-6-methylene-decahydronaphthalen-1-ylmethanol (1f). To a solution of 200 mg (0.38 mmol) of **1e** in dry ether was added a suspension of 100 mg (2.6 mmol) of $LiAlH_4$ in dry ether. The mixture was stirred at room temperature under argon for 5 h. The excess of hydride was decomposed with wet ether, then it was acidified with 2 N HCl and extracted with ether. After being dried over Na_2SO_4 and evaporation of the solvent, it gave a reaction product which was purified by column chromatography (Hex/EtOAc 1:1) to yield 90 mg (60%) of **1f**. mp 122−124 °C (Hex−EtOAc). $[\alpha]^{22}_D$ +41.8° (*c*, 0.93). UV λ_{max} (ϵ): 290(6800). IR cm^{-1}: 3500, 3400, 1660, 1600, 1490.^{1}H NMR ($CDCl_3$) δ: 0.67 (*s*, 3H, H-11), 0.93 (*s*, 3H, H-10), 0.90−2.00 (*m*, 14H, H-2, 3, 4, 5, 7, 8, 8a, 1′, 2′), 2.20 (*m*, 1H, H-7), 2.45 (*m*, 1H, H-4), 3.18 (*m*, 2H, H-1″), 3.28 (*bs*, 2H, H-4″), 3.25 (*d*, 1H, *J* = 10.9, H-9a), 3.70 (*d*, 1H, *J* = 10.9, H-9b), 4.58 (*bs*, 1H, H-12a), 4.84 (*bs*, 1H, H-12b), 5.54 (*bs*, 1H, H-3″), 6.45 (*s*, 2H, H-7″ and H-6″). ^{13}C NMR ($CDCl_3$) δ: 15.9(C-11), 20.0(C-3), 23.0(C-1′), 25.6(C-4″), 26.3(C-8), 27.8(C-10), 28.6(C-1″), 36.5(C-2′), 37.4-(C-2), 39.6(C-4a), 39.9(C-7), 40.3(C-1), 40.6(C-4), 57.7(C-8a and C-5), 65.0(C-9), 107.1(C-12), 113.0(C-7″ and C-6″), 118.8(C-3″), 123.6(C-4a″), 124.0(C-8a″), 136.4(C-2″), 148.4(C-8″ and C-5″), 149.6(C-6). HRMS (FAB-POSI, M + 1) calcd 397.2742, found 397.2756.

(1*S*,4a*R*,5*S*,8a*R*)-5-[2′-(9″,10″-Dioxo-1″,4″,4a″,9″,9a″,10″-hexahydryl]-1,4a-dimethyl-6-methylene-decahydronaphthalen-1-ylmethyl Acetate (5e). From the reaction product between myrceocommunyl acetate (330 mg, 1.08 mmol) and 1,4-naphthoquinone (170 mg, 1.08 mmol) was isolated 220 mg (42%) of **5e** (Hex/EtOAc 7:3). $[\alpha]^{22}_D$ +25.5° (*c*, 0.57). UV λ_{max} (ϵ): 223(11300), 252(11000). IR cm^{-1}: 1740, 1690, 1650, 1600, 1450, 1240. ^{1}H NMR ($CDCl_3$) δ: 0.65 (*s*, 3H, H-11), 0.96, (*s*, 3H, H-10), 2.01 (*s*, 3H, OAc), 0.90−2.50 (*m*, 16H, H-2, 3, 4, 5, 7, 8, 8a, 1′, 2′), 3.40 (*m*, 6H, H-4″, 1″, 9a″, 4a″), 3.81 (*d*, 1H, *J* = 11.0, H-9a), 4.18 (*d*, 1H, *J* = 11.0, H-9b), 4.47 (*bs*, 1H, H-12a), 4.79 (*bs*, 1H, H-12b), 5.39 (*bs*, 1H, H-3″), 7.73 (*m*, 2H, H.7″and 6″), 8.03 (*m*, 2H, H-8″ and H-5″). ^{13}C NMR ($CDCl_3$) δ: 15.3(CH_3), 19.0(CH_2), 20.9($OCOCH_3$), 21.3(CH_2), 24.6(CH_2), 24.9(CH_2), 27.6(CH_2 and CH_3), 36.3(CH_2), 37.4(C), 38.5(2 × CH_2), 39.0(CH_2), 39.5(C), 46.5(CH), 47.2(CH), 55.6(CH), 56.3-(CH), 66.8(CH_2), 106.7(CH_2), 118.0(CH), 126.8(2 × CH), 134.2-(C and 2 × CH), 135.8(C), 136.2(C), 147.8(C), 171.2($OCOCH_3$), 187.1(2 × *C*O). Anal. ($C_{32}H_{40}O_4$) C, H. HRMS (FAB-POSI, M + 1) calcd 487.2848, found 487.2876.

(1*S*,4a*R*,5*S*,8a*R*)-5-[2′-(5″,8″-Diacetoxy-naphthalen-2″-yl)-ethyl]-1,4a-dimethyl-6-methylene-decahydronaphthalene-1-carboxylic Acid (4b). General Procedure for the Aromatization with DDQ. To a solution of **1b** (170 mg, 0.34 mmol) in dry ether was added DDQ (114 mg, 0.52 mmol). The mixture was kept at room temperature for 0.5−1 h. Then it was filtered, the organic solvent was evaporated, and the product was purified by CC, using mixtures of Hex/EtOAc 7:3 as eluent, to yield 100 mg (60%) of **4b**. $[\alpha]^{22}_D$ +39.1° (*c*, 0.94). UV λ_{max} (ϵ): 226(11800), 257(2200). IR cm^{-1}: 3500, 1770, 1730, 1640, 1470. ^{1}H NMR ($CDCl_3$) δ: 0.62 (*s*, 3H, H-11), 1.20 (*s*, 3H, H-10), 2.44 (*s*, 3H, OAc), 2.47 (*s*, 3H, OAc), 0.90−2.50 (*m*, 14H, H-2, 3, 4, 5, 7, 8, 8a, 1′), 2.55 (*m*, 1H, H-2′), 2.90 (*m*, 1H, H-2′), 4.69 (*bs*, 1H, H-12a), 4.88 (*bs*, 1H, H-12b), 7.18 (*s*, 1H, H-7″), 7.19 (*s*, 1H, H-6″), 7.39 (*dd*, 1H, J_1 = 8.6, J_2 = 1.7, H-3″), 7.62 (*d*, 1H, *J* = 1.7, H-1″), 7.77 (*d*, 1H, *J* = 8.6, H-4″). ^{13}C NMR ($CDCl_3$) δ: 12.9(C-11), 19.1(C-3), 20.9(2 × $OCOCH_3$), 25.3(C-1′), 26.2(C-8), 28.9(C-10), 34.8(C-2′), 38.0(C-2), 38.8(C-7), 39.1(C-4), 40.5(C-4a), 44.7(C-1), 55.2(C-5), 56.3(C-8a), 106.8-(C-12), 116.6(C-6″), 117.6(C-7″), 120.0(C-1″), 121.7(C-4″), 126.3-(C-4a″), 128.0(C-8a″), 128.5(C-3″, 141.9(C-2″), 144.4(C-8″ and C-5″), 148.0(C-6), 169.1(2 × $OCOCH_3$), 184.0(C-9). Anal. ($C_{30}H_{36}O_6$) C, H. HRMS (FAB-POSI, M + 1) calcd 493.2590, found 493.2541.

(1*S*,4a*R*,5*S*,8a*R*)-5-[2′-(5″,8″-Diacetoxy-naphthalen-2″-yl)-ethyl]-1,4a-dimethyl-6-methylene-decahydronaphthalene-1-carboxylic Acid Methyl Ester (4d). Obtained from **1d** (65%). $[\alpha]^{22}_D$ +42.3° (*c*, 0.85). UV λ_{max} (ϵ): 224(12000), 254(1800). IR cm^{-1}: 1770, 1730, 1625, 1470. GCMS (220−290 °C, 5 °C/min, HP-1 column), >99%, t_R = 23.92 min, (*m*/*z*) 506 (M^+). ^{1}H NMR ($CDCl_3$) δ: 0.52 (*s*, 3H, H-11), 1.18 (*s*, 3H, H-10), 2.45 (*s*, 3H, OAc), 2.47 (*s*, 3H, OAc), 0.90−2.50 (*m*, 14H, H-2, 3, 4, 5, 7, 8, 8a, 1′), 2.60 (*m*, 1H, H-2′), 2.90 (*m*, 1H, H-2′), 3.61 (*s*, 3H, OCH_3), 4.69 (*bs*, 1H, H-12a), 4.98 (*bs*, 1H, H-12b), 7.20 (*s*, 2H, H-7″ and H-6″), 7.39 (*dd*, 1H, J_1 = 8.7, J_2 = 1.6, H-3″), 7.56 (*d*, 1H, *J* = 1.6, H-1″), 7.80 (*d*, 1H, *J* = 8.7, H-4″). ^{13}C NMR ($CDCl_3$) δ: 12.7(C-11), 20.1(C-3), 20.9(2 × $OCOCH_3$), 25.3(C-1′), 26.4(C-8), 28.8(C-10), 34.9(C-2′), 38.2(C-2), 38.9(C-7), 39.2(C-4), 40.4(C-4a), 44.5(C-1), 51.0(C-5), 55.3(OMe), 56.4-(C-8a), 106.5(C-12), 116.7(C-6″), 117.6(C-7″), 120.0(C-1″), 121.7-(C-4″), 126.3(C-4a″), 128.0(C-8a″), 28.5(C-3″), 141.9(C-2″), 144.0(C-8″), 144.2(C-5″), 148.2(C-6), 169.1(2 × $OCOCH_3$), 177.6(C-9). Anal. ($C_{31}H_{38}O_6$) C, H. HRMS (FAB-POSI, M + 1) calcd 507.2746, found 507.2752.

(1*S*,4a*R*,5*S*,8a*R*)-5-[2′-(9″,10″-Dioxo-9″,10″-dihydroanthracen-2″-yl)-ethyl]-1,4a-dimethyl-6-methylene-decahydronaphthalen-1-ylmethyl Acetate (6e). Prepared from **5e** (70%). $[\alpha]^{22}_D$ +22.5° (*c*, 0.90). UV λ_{max} (ϵ): 243(29800), 325-(4100). IR cm^{-1}: 1740, 1680, 1600, 1300, 1240. GCMS (220−290 °C, 5 °C/min, SPB-1 column), >99%, t_R = 42.50 min, (*m*/*z*) 484 (M^+). ^{1}H NMR ($CDCl_3$) δ: 0.70 (*s*, 3H, H-11), 0.94, (*s*, 3H, H-10), 2.03 (*s*, 3H, OAc), 0.90−2.00 (*m*, 12H, H-2, 3, 4, 5, 7, 8, 8a, 1′), 2.45 (*m*, 1H, H-7), 2.50 (*m*, 1H, H-4), 2.55 (*m*, 1H, H-2′), 2.90 (*m*, 1H, H-2′), 3.84 (*d*, 1H, *J* = 11.0, H-9a), 4.20 (*d*, 1H, *J* = 11.0, H-9b), 4.67 (*s*, 1H, H-12a), 4.95 (*s*, 1H, H-12b), 7.58 (*dd*, 1H, J_1 = 7.9, J_2 = 1.9, H-3″), 7.80 (*m*, 2H, H-7″ and 6″), 8.09 (*d*, H, *J* = 1.9, H-1″), 8.23 (*d*, 1H, *J* = 7.9, H-4″), 8.31 (*m*, 2H, H-8″and H-5″). ^{13}C NMR ($CDCl_3$) δ: 15.3(CH_3), 19.0-(CH_2), 20.9($OCOCH_3$), 24.6(CH_2), 25.4(CH_2), 27.5(CH_3), 35.0-(CH_2), 36.3(CH_2), 37.4 (C), 38.6(CH_2), 39.0(CH_2), 39.7(C), 56.3(2 × CH), 66.8(CH_2), 107.1(CH_2), 126.9(CH), 127.2(2 × CH), 127.6(CH), 131.4 (C) 133.9(2 × CH), 134.0 (3 × C), 134.3(CH), 147.6(C), 150.4(C), 171.1($OCOCH_3$), 183.0 (CO), 183.5(CO). Anal. ($C_{32}H_{36}O_4$) C, H. HRMS (FAB-POSI, M + 1) calcd 485.2691, found 485.2705.

(1*S*,4a*R*,5*S*,8a*R*)-5-[2′-(5″,8″-Dioxo-5″,8″-dihydronaphthalen-2″-yl)-ethyl]-1,4a-dimethyl-6-methylene-decahydronaphthalen-1-ylmethyl Acetate (3e) and (1*S*,4a*R*,5*S*,-8a*R*)-5-[2′-(5″,8″-Diacetoxy-naphthalen-2″-yl)-ethyl]-1,4a-dimethyl-6-methylene-decahydronaphthalen-1-ylmethyl Acetate (4e). The cycloaddition product between myrceocommunyl acetate (350 mg, 1.03 mmol) and *p*-benzoquinone (115 mg, 1.06 mmol) was acetylated and treated with DDQ as described above. Column chromatography of the reaction product yielded 64 mg (13%) of **3e** and 93 mg (16%) of **4e**.

3e: $[\alpha]^{22}_D$ +27.8° (*c*, 0.23). IR cm^{-1}: 1740, 1670, 1600, 1240. GCMS (150−300 °C, 10 °C/min, SPB-1 column), >99%, t_R = 23.55 min, (*m*/*z*) 434 (M^+). ^{1}H NMR ($CDCl_3$) δ: 0.67 (*s*, 3H, H-11), 0.94 (*s*, 3H, H-10), 2.02 (*s*, 3H, OAc), 0.90−2.00 (*m*, 12H, H-2, 3, 4, 5, 7, 8, 8a, 1′), 2.40 (*m*, 1H, H-7), 2.45 (*m*, 1H, H-4), 2.55 (*m*, 1H, H-2′), 2.90 (*m*, 1H, H-2′), 3.83 (*d*, 1H, *J* = 10.9, H-9a), 4.19 (*d*, 1H, *J* = 10.9, H-9b), 4.63 (*bs*, 1H, H-12a), 4.93 (*bs*, 1H, H-12b), 6.94 (*s*, 2H, H-7″ and H-6″), 7.53 (*dd*, 1H, J_1 = 8.0, J_2 = 1.8, H-3″), 7.85 (*d*, 1H, *J* = 1.5, H-1″), 7.99 (*d*, 1H, *J* = 8.0, H-4″). ^{13}C NMR ($CDCl_3$) δ: 15.2(C-11), 18.8(C-3), 21.0 ($OCOCH_3$), 24.4(C-1′), 25.3(C-8), 27.5(C-10), 34.8(C-2′), 36.1-(C-2), 37.3(C-4a), 38.4(C-7), 38.8(C-4), 39.5(C-1), 56.1(C-8a and C-5), 66.7(C-9), 107.1(C-12), 126.1(C-1″), 126.7(C-4″), 129.9-(C-4a″), 131.9(C-8a″), 134.0(C-3″), 138.5(C-6″), 138.7(C-7″), 147.4(C-2″), 150.3(C-6), 171.3($OCOCH_3$), 184.9(C-5″), 185.4-(C-8″). HRMS (M^+) calcd 434.2457, found 434.2398.

4e: $[\alpha]^{22}_D$ +13.2° (*c*, 0.62). IR cm^{-1}: 1770, 1740, 1240, 1050. GCMS(100−300 °C, 10 °C/min, SPB-1 column), >99%, t_R = 33.01 min, (*m*/*z*) 520 (M^+). ^{1}H NMR ($CDCl_3$) δ: 0.69 (*s*, 3H, H-11), 0.93 (*s*, 3H, H-10), 2.02 (*s*, 3H, OAc), 0.90−2.00 (*m*, 13H,

H-2, 3, 4, 5, 7, 8, 8a, 1′), 2.40 (*m*, 1H, H-4), 2.44 (*s*, 3H, OAc), 2.46 (*s*, 3H, OAc), 2.60 (*m*, 1H, H-2′), 2.90 (*m*, 1H, H-2′), 3.83 (*d*, 1H, J = 10.9, H-9a), 4.21 (*d*, 1H, J = 10.9, H-9b), 4.68 (*bs*, 1H, H-12a), 4.95 (*bs*, 1H, H-12b), 7.15 (*d*, 1H, J = 8.0, H-7″), 7.21 (*d*, 1H, J = 8.0, H-6″), 7.37 (*d*, 1H, J = 8.8, H-3″), 7.55 (*bs*, 1H, H-1″), 7.78 (*d*, 1H, J = 8.8, H-4″). ^{13}C NMR ($CDCl_3$) δ: 15.2(C-11), 18.8(C-3), 20.9(3 × OCO*C*H$_3$), 24.4(C-1′), 25.1-(C-8), 27.3(C-10), 34.5(C-2′), 35.9(C-2), 37.1(C-4a), 38.4(C-7), 38.5(C-4), 39.4(C-1), 55.5(C-5), 55.9(C-8a), 66.6(C-9), 106.8(C-12), 116.6(C-6″), 117.6(C-7″), 119.8(C-1″), 121.5 (C-4″), 126.1-(C-4a″), 127.7 (C-8a″) 128.4(C-3″), 141.8 (C-2″), 143.8 (C-8″), 144.2 (C-5″), 147.6 (C-6), 169.3 (2 × O*C*OCH$_3$), 171.2 (O*C*OCH$_3$). Anal. ($C_{32}H_{40}O_6$) C, H. HRMS (FAB-POSI, M + 1) calcd 521.2903, found 521.2916.

(1*S*,4a*R*,5*S*,8a*R*)-5-[2′-(2″,3″-Epoxy-5″,8″-dihydroxy-1″,2″,3″,4″-te′-yl)-ethyl]-1,4a-dimethyl-6-methylene-decahydronaphthalene-1-carboxylic Acid Methyl Ester (7c). General Procedure for the Epoxidation of Double Bonds. A total of 337 mg (0.80 mmol) of **1c** was dissolved in dichloromethane and MCPBA (138 mg, 0.80 mmol) in the presence of $NaHCO_3$ (192 mg). The mixture was kept at room temperature for 1 h. Then dichloromethane was added, followed by 10% aqueous $Na_2S_2O_3$ until the oxidant was eliminated. The organic layer was washed with water and dried over Na_2SO_4, and the solvent evaporated. The reaction product was purified by CC (Hex/EtOAc 6:4), and 266 mg (64%) of **7c** was obtained. UV λ_{max} (ϵ): 292(5800). IR cm^{-1}: 3400, 1725, 1650, 1600, 1470, 1230. ^{1}H NMR ($CDCl_3$) δ: 0.50 (*s*, 3H, H-11), 1.17 (*s*, 3H, H-10), 1.00−2.50 (*m*, 14H, H-2, 3, 4, 5, 7, 8, 8a, 1′), 2.70−3.50 (*m*, 6H, H-2′, 4″, 1″), 3.39 (*bs*, 1H, H-3″), 3.61 (*s*, 3H, OCH$_3$), 4.51 (*bs*, 1H, H-12a), 4.82 (*bs*, 1H, H-12b), 6.43 (*s*, 2H, H-7″ and H-6″). ^{13}C NMR ($CDCl_3$) δ: 13.3(C-11), 20.0-(C-3), 21.1(C-1′), 25.4(C-4″), 27.2(C-1″), 27.6(C-8), 29.2(C-10), 36.4(C-2′), 39.3(C-2), 39.9(C-7), 40.4(C-4), 41.5(C-4a), 45.6(C-1), 51.3(OCH$_3$), 56.6(C-5), 57.2(C-3″), 57.7(C-8a), 59.5(C-2″), 107.2(C-12), 113.0(C-6″), 113.5(C-7″), 123.0(C-4a″), 123.5(C-8a″), 149.0(C-6 and C-5″), 149.2(C-8″), 179.4(C-9).

(1*S*,4a*R*,5*S*,8a*R*)-5-[2′-(5″,8″-Diacetoxy-2″,3″-epoxy-1″,2″,3″,4″-te′-yl)-ethyl]-1,4a-dimethyl-6-methylene-decahydronaphthalene-1-carboxylic Acid Methyl Ester (7d). Epoxidation of **1d** yielded **7d** (74%) (Hex/EtOAc 7:3). UV λ_{max} (ϵ): 262(4380). IR cm^{-1}: 1770, 1725, 1640, 1470. ^{1}H NMR ($CDCl_3$) δ: 0.51 (*s*, 3H, H-11), 1.18 (*s*, 3H, H-10), 2.32 (*s*, 3H, OAc), 2.33 (*s*, 3H, OAc), 1.00−2.50 (*m*, 14H, H-2, 3, 4, 5, 7, 8, 8a, 1′), 2.70−3.32 (*m*, 6H, H-2′, 4″, 1″), 3.62 (*s*, 3H, OCH$_3$), 4.50 (*s*, 1H, H-12a), 4.88 (*s*, 1H, H-17b), 3.25 (*t*, 1H, J = 6, H-3″), 6.93 (*s*, 2H, H-7″ and H-6″). ^{13}C NMR ($CDCl_3$) δ: 12.6-(C-11), 18.7 (C-3), 20.1(C-1′), 20.8(2 × OCO*C*H$_3$), 25.0(C-4″), 26.4(C-8), 27.3(C-1″), 28.9(C-10), 34.9(C-2′), 38.3(C-2), 38.8-(C-7), 39.3(C-4), 40.5(C-4a), 44.4(C-1), 51.1(OCH$_3$), 55.9(C-5), 56.2(C-8a), 58.2(C-3″), 59.1(C-2″), 106.7(C-12), 120.3(C-7″ and C-6″), 125.8(C-4a″), 126.7(C-8a″), 146.6(C-5″), 146.7(C-8″), 147.8(C-6), 168.8(2 × O*C*OCH$_3$), 177.6(C-9). Anal. ($C_{31}H_{40}O_7$) C, H.

(1*S*,4a*R*,5*S*,8a*R*)-5-[2′-(5″,8″-Diacetoxy-naphthalen-2″-yl)-ethyl]-1,4a-dimethyl-6,6-(α-epoxy-methano)-decahydronaphthalene-1-carboxylic Acid Methyl Ester (8) and (1*S*,4a*R*,5*S*,8a*R*)-5-[2′-(5″,8″-Diacetoxy-naphthalen-2″-yl)-ethyl]-1,4a-dimethyl-6,6-(β-epoxymethano)-decahydronaphthalene-1-carboxylic Acid Methyl Ester (9). Epoxidation of 725 mg (1.43 mmol) of **4d** with MCPBA (485 mg, 2.81 mmol) for 5 h yielded a crude that was purified by CC with $CHCl_3$/EtOAc (95:5) to obtain the following compounds:

(a) 413 mg (55%) of **8**. $[\alpha]^{22}_D$ +28.9° (*c*, 1.38). UV λ_{max} (ϵ): 286 (5900). IR cm^{-1}: 1770, 1720, 1200 and 1180. GCMS (220−290 °C, 5 °C/min, HP-1 column), >99%, t_R = 27.80 min, (*m*/*z*) 522 (M$^+$). ^{1}H NMR ($CDCl_3$) δ: 0.63 (*s*, 3H, H-11), 1.20 (*s*, 3H, H-10), 1.00−2.30 (*m*, 14H, H-2, 3, 4, 5, 7, 8, 8a, 1′), 2.44 (*s*, 3H, OAc), 2.47 (*s*, 3H, OAc), 2.56 (*d*, 1H, J = 4.4, H-12b), 2.72 (*m*, 1H, H-2′), 2.79 (*d*, 1H, J = 4.4, H-12a), 2.90 (*m*, 1H, H-2′), 3.64 (*s*, 3H, OCH$_3$), 7.16 (*d*, 1H, J = 8.2, H-6″), 7.19 (*d*, 1H, J = 8.2, H-7″), 7.38 (*dd*, 1H, J_1 = 8.6, J_2 = 1.6, H-3″), 7.61 (*d*, 1H, J = 1.6, H-1″), 7.77 (*d*, 1H, J = 8.6, H-4″). ^{13}C NMR ($CDCl_3$) δ: 12.9(C-11), 19.4(C-3), 21.0(2 × OCO*C*H$_3$), 23.5(C-1′), 24.1(C-8), 28.8(C-10), 36.9(C-7), 37.7(C-2′), 37.9(C-2), 39.2-(C-4), 40.7(C-4a), 44.1(C-1), 50.3(C-12), 51.2 (OCH$_3$), 52.4(C-5), 55.7(C-8a), 58.9(C-6), 116.7(C-6″), 117.6(C-7″), 120.1(C-1″), 121.6(C-4″), 126.2(C-4a″), 127.8(C-8a″), 128.7(C-3″), 141.7(C-2″), 144.0(C-8″), 144.3(C-5″), 169.3(2 × O*C*OCH$_3$), 177.5(C-9). Anal. ($C_{31}H_{38}O_7$) C, H. HRMS (M+) calcd 522.2617, found 522.2559.

(b) 84 mg (11%) of mixture of **8** and **9**.

(c) 94 mg (13%) of **9**. $[\alpha]^{22}_D$ +34.1° (*c*, 1.26). UV λ_{max} (ϵ): 286-(5300). IR cm^{-1}: 1770, 1720, 1200 and 1180. GCMS (220−290 °C, 5 °C/min, HP-1 column), >99%, t_R = 29.79 min, (*m*/*z*) 522 (M$^+$). ^{1}H NMR ($CDCl_3$) δ: 0.63 (*s*, 3H, H-11), 1.20 (*s*, 3H, H-10), 0.80−2.20 (*m*, 14H, H-2, 3, 4, 5, 7, 8, 8a, 1′), 2.43 (*s*, 3H, OAc), 2.45 (*d*, 1H, J = 4.0, H-12b), 2.46 (*s*, 3H, OAc), 2.62 (*m*, 1H, H-2′), 2.73 (*d*, 1H, J = 4.0, H-12a), 2.75 (*m*, 1H, H-2′), 3.63 (*s*, 3H, OCH$_3$), 7.18 (*d*, 1H, J = 8.2, H-6″), 7.22 (*d*, 1H, J = 8.2, H-7″), 7.35 (*dd*, 1H, J_1 = 8.7, J_2 = 1.7, H-3″), 7.55 (*d*, 1H, J = 1.7, H-1″), 7.78 (*d*, 1H, J = 8.6, H-4″). ^{13}C NMR ($CDCl_3$) δ: 12.7(C-11), 19.1(C-3), 21.0(2 × OCO*C*H$_3$), 21.9(C-1′), 22.9(C-8), 28.6(C-10), 36.1(C-7), 37.9(C-2), 38.1(C-2′), 38.9-(C-4), 40.2(C-4a), 44.1(C-1), 49.4(C-12), 51.2(C-5 and OCH$_3$), 55.8(C-8a), 57.3(C-6), 116.9(C-6″), 117.8(C-7″), 119.9(C-1″), 121.8(C-4″), 126.3(C-4a″), 127.8(C-8a″), 128.3(C-3″), 140.9(C-2″), 143.9(C-8″), 144.3(C-5″), 169.3(2 × O*C*OCH$_3$), 177.6(C-9). Anal. ($C_{31}H_{38}O_7$) C, H. HRMS (M+) calcd 522.2617, found 522.2604.

(1*S*,4a*R*,5*S*,6*S*,8a*R*)-5-[2′-(5″,8″-Diacetoxy-naphthalen-2″-yl)-ethyl]-6-formyl-1,4a-dimethyl-decahydronaphthalene-1-carboxylic Acid Methyl Ester (10) and (1*S*,-4a*R*,5*S*,6*R*,8a*R*)-5-[2′-(5″,8″-Diacetoxy-naphthalen-2″-yl)-ethyl]-6-formyl-1,4a-dimethyl-decahydronaphthalene-1-carboxylic Acid Methyl Ester (11). To a solution of 230 mg (0.44 mmol) of a mixture of epoxides **8** and **9** in dry benzene was added 0.83 mL (6.5 mmol) of BF_3−Et_2O. The mixture was stirred at room temperature for 45 min. Then the solvent was removed, and the crude was dissolved in ether, washed with 10% aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4, and the solvent evaporated. The reaction crude was chromatographed with Hex/acetone (7:3) to yield the following compounds:

(a) 35 mg (15%) of **10**: $[\alpha]^{22}_D$ +35.4° (*c*, 0.13). IR cm^{-1}: 1770, 1720, 1200, 1180 and 1050. ^{1}H NMR ($CDCl_3$) δ: 0.66 (*s*, 3H, H-11), 1.19 (*s*, 3H, H-10), 0.9−2.40 (*m*, 14H, H-2, 3, 4, 5, 7, 8, 8a, 1′), 2.35 (*m*, 1H, H-6), 2.45 (*s*, 3H, OAc), 2.48 (*s*, 3H, OAc), 2.60 (*m*, 1H, H-2′), 2.80 (*m*, 1H, H-2′), 3.64 (*s*, 3H, OCH$_3$), 7.17 (*d*, 1H, J = 8.2, H-6″), 7.21 (*d*, 1H, J = 8.2, H-7″), 7.32 (*dd*, 1H, J_1 = 8.7, J_2 = 1.7, H-3″), 7.53 (*d*, 1H, J = 1.7, H-1″), 7.77-(*d*, 1H, J = 8.7, H-4″), 9.57 (*d*, 1H, J = 4.6, H-12). ^{13}C NMR ($CDCl_3$) δ: 12.4(C-11), 19.2(C-3), 21.0(2 × OCO*C*H$_3$), 21.6(C-1′), 27.3(C-8), 28.7(C-10), 31.3(C-7), 37.0(C-2′), 38.0(C-2), 38.2-(C-4a), 38.7(C-4), 44.0(C-1), 49.5(C-6), 51.3(OCH$_3$), 54.0(C-5), 55.4(C-8a), 116.9(C-6″), 117.8(C-7″), 120.1(C-1″), 121.8(C-4″), 126.2(C-4a″), 127.8(C-8a″), 128.3(C-3″), 141.0(C-2″), 144.0(C-8″), 144.3(C-5″), 169.3(2 × O*C*OCH$_3$), 177.5(C-9), 205.0(C-12). Anal. ($C_{31}H_{38}O_7$) C, H. HRMS (FAB-POSI, M + 1) calcd 523.2695, found 523.2668.

(b) 140 mg (61%) of **10** and **11**.

(c) 14 mg (6%) of **11**: $[\alpha]^{22}_D$ +22.6° (*c*, 0.23). IR cm^{-1}: 1770, 1720, 1200, 1180 and 1050. GCMS (150−300 °C, 10 °C/min, SPB-1 column), >99%, t_R = 31.62 min, (*m*/*z*) 522 (M$^+$). ^{1}H NMR ($CDCl_3$) δ: 0.59 (*s*, 3H, H-11), 1.16 (*s*, 3H, H-10), 0.9−2.40 (*m*, 14H, H-2, 3, 4, 5, 7, 8, 8a, 1′), 2.45 (*s*, 3H, OAc), 2.48 (*s*, 3H, OAc), 2.60 (*m*, 1H, H-6), 2.70 (*m*, 1H, H-2′), 3.06 (*m*, 1H, H-2′), 3.61 (*s*, 3H, OCH$_3$), 7.19 (*d*, 1H, J = 8.2, H-6″), 7.22 (*d*, 1H, J = 8.2, H-7″), 7.41 (*dd*, 1H, J_1 = 8.7, J_2 = 1.6, H-3″), 7.60 (*d*, 1H, J = 1.6, H-1″), 7.81(*d*, 1H, J = 8.7, H-4″), 10.07 (*bs*, 1H, H-12). ^{13}C NMR ($CDCl_3$) δ: 13.6(C-11), 19.2(C-3), 20.3(C-1′), 21.0(2 × OCO*C*H$_3$), 26.8(C-7), 27.0(C-8), 28.6(C-10), 34.4(C-2′), 37.9(C-2), 38.6(C-4a), 38.7(C-4), 43.8(C-1), 46.6(C-6), 51.2-(OCH$_3$), 52.0(C-5), 56.1(C-8a), 116.9(C-6″), 117.8(C-7″), 120.0-(C-1″), 121.9(C-4″), 126.3(C-4a″), 127.8(C-8a″), 128.2(C-3″), 140.9(C-2″), 143.9(C-8″), 144.3(C-5″), 169.4(2 × O*C*OCH$_3$), 177.6(C-9), 205.1(C-12). Anal. ($C_{31}H_{38}O_7$) C, H. HRMS (FAB-POSI, M + 1) calcd 523.2695, found 523.2654.

(1*S*,4a*R*,5*S*,6*S*,8a*R*)-5-[2′-(5″,8″-Diacetoxy-naphthalen-2″-yl)-ethyl]-6-hydroxymethyl-1,4a-dimethyl-decahydronaphthalene-1-carboxylic Acid Methyl Ester (12) and (1*S*,4a*R*,5*S*,6*R*,8a*R*)-5-[2′-(5″,8″-Diacetoxy-naphthalen-2″-yl)-ethyl]-6-hydroxymethyl-1,4a-dimethyl-decahydronaphthalene-1-carboxylic Acid Methyl Ester (13). A total of 118 mg (0.23 mmol) of the mixture of **10** and **11** was dissolved in 15 mL of dry THF, and 4.3 mg (0.11 mmol) of $NaBH_4$ was added. The reaction mixture was stirred at room temperature over 6 h. After this time, it was acidified with 2 N HCl, extracted with EtOAc, washed with brine, and dried over Na_2SO_4. The crude was purified by CC with $CHCl_3$/EtOAc (85:15), obtaining the following compounds:

(a) 9 mg (7%) of **12**. $[\alpha]^{22}_D$ +10.0° (*c*, 0.45). UV λ_{max} (ϵ): 286 (4700). IR cm^{-1}: 3440, 1770, 1720, 1200, 1050 and 820. GCMS (220−290 °C, 5 °C/min, HP-1 column), >99%, t_R = 27.91 min, (*m*/*z*) 524 (M^+). ^{1}H NMR ($CDCl_3$) δ: 0.62 (*s*, 3H, H-11), 1.18 (*s*, 3H, H-10), 0.90−2.20 (*m*, 15H, H-2, 3, 4, 5, 6, 7, 8, 8a, 1′), 2.45 (*s*, 3H, OAc), 2.47 (*s*, 3H, OAc), 2.65 (*m*, 1H, H-2′), 2.80 (*m*, 1H, H-2′), 3.63 (*s*, 3H, OCH_3), 3.80 (*m*, 2H, H-12), 7.16 (*d*, 1H, *J* = 8.2, H-6″), 7.21 (*d*, 1H, *J* = 8.2, H-7″), 7.40 (*dd*, 1H, J_1 = 8.8, J_2 = 1.8, H-3″), 7.58 (*d*, 1H, *J* = 1.8, H-1″), 7.77 (*d*, 1H, *J* = 8.8, H-4″). ^{13}C NMR ($CDCl_3$) δ: 12.2(C-11), 19.4(C-3), 21.0(2 × OCO*C*H$_3$), 22.9(C-1′), 28.7(C-10), 31.1 (C-8 and C-7), 38.2(C-2 and C-2′), 38.6(C-4a), 39.0(C-4), 41.8(C-6), 44.1(C-1), 51.0(OCH_3), 51.4(C-5), 56.0(C-8a), 66.2(C-12), 116.8(C-6″), 117.7(C-7″), 119.8(C-1″), 121.7(C-4″), 126.2(C-4a″), 127.8(C-8a″), 128.5(C-3″), 141.8(C-2″), 144.0(C-8″), 144.3(C-5″), 169.4 (2 × O*C*OCH$_3$), 177.9(C-9). Anal. ($C_{31}H_{40}O_7$) C, H. HRMS (FAB-POSI, M + 1) calcd 525.2852, found 525.2869.

(b) 69 mg (57%) of **12** and **13**.

(c) 10 mg (8%) of **13**. $[\alpha]^{22}_D$ +21.0° (*c*, 0.50). UV λ_{max} (ϵ): 284 (4800). IR cm^{-1}: 3440, 1770, 1720, 1200, 1050 and 820. GCMS (220−290 °C, 5 °C/min, HP-1 column), >99%, t_R = 28.57 min, (*m*/*z*) 524 (M^+). ^{1}H NMR ($CDCl_3$) δ: 0.54 (*s*, 3H, H-11), 1.16 (*s*, 3H, H-10), 0.90−2.15 (*m*, 15H, H-2, 3, 4, 5, 6, 7, 8, 8a, 1′, 2′), 2.46 (*s*, 3H, OAc), 2.47 (*s*, 3H, OAc), 2.65 (*m*, 1H, H-2′), 2.90 (*m*, 1H, H-2′), 3.63 (*s*, 3H, OCH_3), 3.75 (*m*, 2H, H-12), 7.17 (*d*, 1H, *J* = 8.0, H-6″), 7.22 (*d*, 1H, *J* = 8.0, H-7″), 7.39 (*dd*, 1H, J_1 = 8.8, J_2 = 1.8, H-3″), 7.60 (*d*, 1H, *J* = 1.8, H-1″), 7.79(*d*, 1H, *J* = 8.8, H-4″). ^{13}C NMR ($CDCl_3$) δ: 13.9(C-11), 19.0(C-3), 19.1(C-1′), 21.0(2 × OCO*C*H$_3$), 27.0 (C-8), 28.7(C-10), 29.7(C-7), 34.4(C-2′), 37.9(C-2), 38.2(C-4a), 39.0(C-6), 39.2-(C-4), 43.8(C-1), 51.1(OCH_3), 51.5(C-5), 56.9(C-8a), 61.0(C-12), 116.8(C-6″), 117.7(C-7″), 119.9(C-1″), 121.7(C-4″), 126.2(C-4a″), 127.8(C-8a″), 128.5(C-3″), 141.5(C-2″), 143.9(C-8″), 144.3(C-5″), 169.4(2 × O*C*OCH$_3$), 177.9(C-9). Anal. ($C_{31}H_{40}O_7$) C, H. HRMS (FAB-POSI, M + 1) calcd 525.2852, found 525.2885.

(1*S*,4a*R*,5*S*,6*S*,8a*R*)-5-[2′-(5″,8″-Diacetoxynaphthalen-2″-yl)-ethyl]-1,4a-dimethyl-decahydro-naphthalene-1,6-dicarboxylic Acid 1-Methyl Ester (14) and (1*S*,4a*R*,5*S*,6*R*,-8a*R*)-5-[2′-(5″,8″-Diacetoxy-naphthalen-2″-yl)-ethyl]-1,4a-dimethyl-decahydronaphthalene-1,6-dicarboxylic Acid 1-Methyl Ester (15). A total of 116 mg (0.22 mmol) of a mixture of **10** and **11** was dissolved in 6 mL of *t*-BuOH and 0.08 mL of 2-methyl-2-butene, and then 0.28 mL of 25% aqueous $NaClO_2$ and 2.4 mL of 5% aqueous NaH_2PO_4 were slowly added. The mixture was kept at room temperature with stirring for 70 h. After this time, 10% aqueous $NaHCO_3$ was added, and the crude was extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4, and the solvent evaporated. The product was purified by flash cromatography with $CHCl_3$/EtOAc (9:1), to afford the following compounds:

(a) 7 mg (6%) of **14**. IR cm^{-1}: 3600−2500, 1770, 1720, 1700, 1200, 1180 and 1050. ^{1}H NMR ($CDCl_3$) δ: 0.60 (*s*, 3H, H-11), 1.17 (*s*, 3H, H-10), 0.80−2.30 (*m*, 14H, H-2, 3, 4, 5, 7, 8, 8a, 1′), 2.41 (*s*, 3H, OAc), 2.46 (*s*, 3H, OAc), 2.70 (*m*, 3H, H-2′, 6), 3.62 (*s*, 3H, OCH_3), 7.16 (*m*, 3H, H-3″, 6″, 7″), 7.44 (*bs*, 1H, H-1″), 7.61 (*d*, 1H, *J* = 8.8, H-4″). ^{13}C NMR ($CDCl_3$) δ: 12.0-(C-11), 19.1(C-3), 21.0(2 × OCO*C*H$_3$), 22.2(C-1′), 28.7(C-10), 31.1(C-8), 31.7(C-7), 37.2(C-2′), 37.9(C-2), 38.4(C-4 and C-4a), 43.9(C-1), 51.1(C-5 and OCH_3), 51.2(C-6), 55.4(C-8a), 116.6-(C-6″), 117.5(C-7″), 120.0(C-1″), 121.5(C-4″), 126.1(C-4a″), 127.6(C-8a″), 128.4(C-3″), 141.3(C-2″), 143.9(C-8″), 144.3(C-5″), 169.3(O*C*OCH$_3$), 169.6 (O*C*OCH$_3$), 177.6(C-9), 182.4(C-12). Anal. ($C_{31}H_{38}O_8$) C, H.

(b) 29 mg (25%) of **14** and **15**.

(c) 5 mg (4%) of **15**. IR cm^{-1}: 3600−2500, 1770, 1720, 1700, 1200, 1180 and 1050. ^{1}H NMR ($CDCl_3$) δ: 0.69 (*s*, 3H, H-11), 1.15 (*s*, 3H, H-10), 0.80−2.40 (*m*, 14H, H-2, 3, 4, 5, 7, 8, 8a, 1′), 2.44 (*s*, 3H, OAc), 2.46 (*s*, 3H, OAc), 2.67 (*m*, 1H, H-2′), 2.87 (*m*, 1H, H-6), 3.11 (*m*, 1H, H-2′), 3.61 (*s*, 3H, OCH_3), 7.17 (*d*, 1H, *J* = 8.2, H-6″), 7.21 (*d*, 1H, *J* = 8.2, H-7″), 7.43 (*dd*, 1H, J_1 = 8.6, J_2 = 1.5, H-3″), 7.60 (*bs*, 1H, H-1″), 7.79 (*d*, 1H, *J* = 8.6, H-4″). ^{13}C NMR ($CDCl_3$) δ: 12.4(C-11), 19.2(C-3), 20.4-(C-1′), 21.0(2 × OCO*C*H$_3$), 27.6(C-8), 28.7(C-10), 29.4(C-7), 34.4(C-2′), 37.9(C-2), 38.8(C-4), 39.1(C-4a), 43.8(C-1), 51.2(C-5 and OCH_3), 51.7(C-6), 56.6(C-8a), 116.7(C-6″), 117.7(C-7″), 119.9(C-1″), 121.7(C-4″), 126.1(C-4a″), 127.8(C-8a″), 128.4(C-3″), 141.7(C-2″), 143.9(C-8″), 144.3(C-5″), 169.4(2 × O*C*OCH$_3$), 177.6 (C-9), 184.9(C-12). Anal. ($C_{31}H_{38}O_8$) C, H.

Molecular Modeling. Initial structures of the epoxide **8** and olefin **4d** were built from suitable fragments and optimized using the MMFF94s force field. From these initial structures, the program ET[19] was used to generate 100 representative and diverse conformations of each of these structures. These conformations were then subjected to energy minimization using the macromodel batchmin 5.5 program to a gradient of less than 0.001 kcal/mol/Å. Each of these sets of 100 conformations was then superimposed on the crystal structure of avarol, using the program SQ with standard parameters, except that the cavity radius was set at 8 Å. One atom of avarol, the less substituted carbon of the double bond, was marked as essential for superposition (type "$", match required by atomic number). Both double bond atoms of avarol were marked with superposition weights of 2.0, the remainder of the atoms being set to weights of 1.0 and of type "*" (match preferred but not essential). Overlays involving conformers with SQ scores within 8 units of the maximum found (112.4 for the epoxide, 110.5 for the olefin) and with energies within 5 kcal/mol of the lowest-energy minimum found (108.9 kcal/mol for the epoxide, 109.6 kcal/mol for the olefin) were considered further. The examples illustrated in the results section were chosen from these overlays as representative.

Bioactivity. Antineoplastic Assays. A screening procedure[15] was used to assess the cytotoxic activity against the following cell lines: P-388 (lymphoid neoplasma from DBA/2 mouse), A-549 (human lung carcinoma), HT-29 (human colon carcinoma), and MEL-28 (human melanoma). Cells were seeded into 16 mm wells (multidishes NUNC 42001) at concentrations of 1 × 10^4 (P-388) and 2 × 10^4 (A-549, HT-29 and MEL-28) cells/well, respectively, in 1 mL aliquots of MEM10FCS medium containing the compound to be evaluated at the concentrations tested. In each case, a set of control wells was incubated in the absence of sample and counted daily to ensure the exponential growth of cells. After 3 days at 37 °C, under a 10% CO_2, 98% humid atmosphere, P-388 cells were observed through an inverted microscopy, and the degree of inhibition was determined by comparison with the controls, whereas A-549, HT-29, and MEL-28 were stained with crystal violet before examination.

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Supporting Information Available: Elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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