Synthesis of new aldehyde derivatives from β-lapachone and nor-β-lapachone

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Dedicated to Professor Edmond A. Rúveda on his 70th birthday

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Abstract

Derivatives **6a** and **6b**, have been obtained in a chemoselective manner by a two step synthesis from β-lapachone (**3a**) and nor-β-lapachone (**3b**), respectively, using CH_2N_2 in ether, which provided the lapachone-epoxide derivatives, **5a** and **5b**, followed by treatment with $BF_3.Et_2O/CH_2Cl_2$. Basic work-up of the reaction mixture of **5a** or **5b** with $BF_3.Et_2O/CH_2Cl_2$ led instead to isolation of the rearranged derivatives **7a** and **7b**, respectively. An *ab initio* theoretical study [B3LYP/6-311+G(d)] on **3a** indicated that the carbon atom, C6, carries a higher positive charge than that at C5 and hence predicts a greater reactivity towards nucleophiles at C6. Another important factor controlling the chemoselectivity in the reaction of **3a** with CH_2N_2 is the steric hindrance of the CH_2 groups of the pyran ring.

Keywords: *beta*-Lapachone, nor-beta-lapachone, epoxides, carbonyl reactivity

Introduction

Several old and new medical problems for mankind are driving research to find improved treatments. Paramount in this area is the research for more potent anticancer, antibacterial and

antibiotic compounds. Compounds with quinonoid derived systems have shown particularly promise. A central feature of ortho and para-quinonoid based cytotoxins is their ability to generate semi-quinone radicals by bioreduction, which then accelerates intracellular hypoxic conditions.[1,2]

The drug arsenal for fighting against tropical diseases includes many natural and synthetic naphthoquinone derivatives, which have been studied extensively due to their abilities to interfere with the bio-activities of enzymes known as *topoisomerases*, a group of enzymes that are critical for DNA replication in cells. In addition, naphthoquinones have been shown to induce what are known as 'reactive oxygen species' that can cause damage to cells. Since the pioneer work of Wendel[1] in 1946, showing that certain 2-hydroxy-3-alkyl-naphthoquinones inhibited the growth of *Plasmodium vivae*, quinones have been the subject of much interest in chemotherapeutic studies, which have proved that the toxicity of naphthoquinones to *Plasmodium sp*. is due to their interaction with the mitochondrial respiratory chain of the parasites.[2] This observation led Fieser and collaborators in the 1940´s to start an extensive search for new quinones for use in malaria chemotherapy.[2] Subsequently, quinones have been studied for antitumor, [2] trypanocidal,[2] molluscicidal,[1] leiscmanicidal,[2] anti-inflammatory[3] and antifungal[4] activities.

Among significant biological active naphthoquinones are atovaquone **1,**[5,6] a coenzyme Q analogue, which inhibits selectively *P. Vivae* by affecting its mitocondrial electron transport and lapachol **2**, a versatile biologically active compound, present in the heartwood of several Tabebuia species from Central and South America, especially *Tabebuia avellanedae Lorentz* ex Grised (Bignoniaceae)[7,8,9], see Figure 1. The principal biological target for lapachol is the P450 reductase enzyme on producing reactive xenobiotics species through a redox cycling-based generation of super-oxide anion radical responsible for DNA scission.[10,11,12]

Another very important quinone is β-lapachone **3a**, a 1,2-naphthoquinone, Figure 1, also found in the heartwood of *Tabebuia sp*, whose extract has been used as a popular medicine for centuries. Recent investigations suggest **3a** has potential application against numerous diseases. Its effectiveness at micromolar concentrations against a variety of cancer cells in cultures indicates its potential against tumor growth. The greatest interest in **3a** is concerned with clinical uses in cancer chemotherapy.[13,14,15] The detailed mechanism of cell death induced by β-lapachone has still to be revealed. It has been discovered that topoisomerases I[16] and II[17], which act directing on DNA, were the biochemical targets involved in the apoptosis, but its role in cell death is not yet clear. Particularly promising is the remarkably powerful synergistic lethality between β-lapachone and taxol against several tumor cell lines implanted into mice.[18] Enhanced lethality of X-rays and alkylating agents to tumor cells in culture was reported when β-lapachone was applied during the recovery period, because of inhibition of DNA lesion repair. [19,20] In addition, β-lapachone also possesses a variety of pharmacological effects, including antibacterial, antifungal, and trypanocidal activities[21]

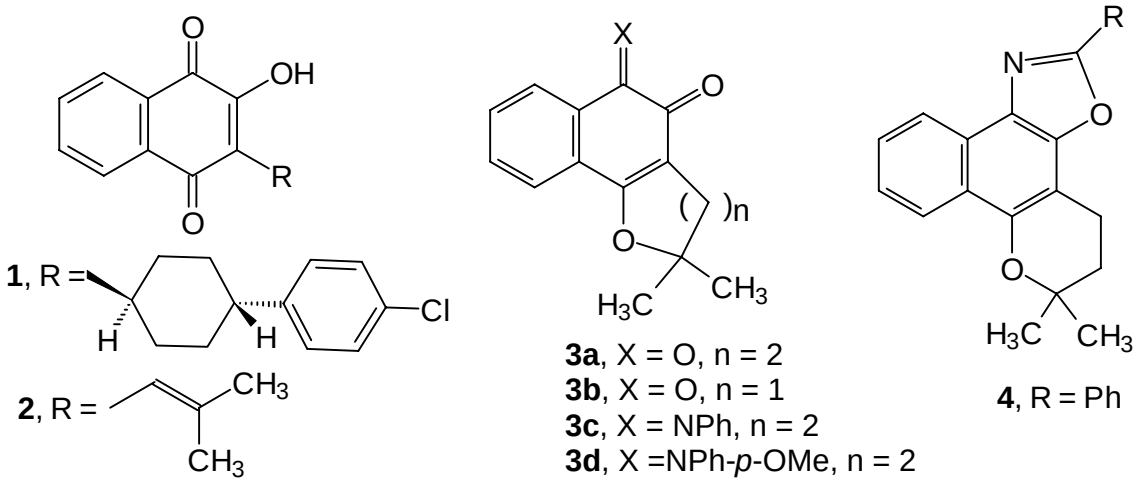


Figure 1

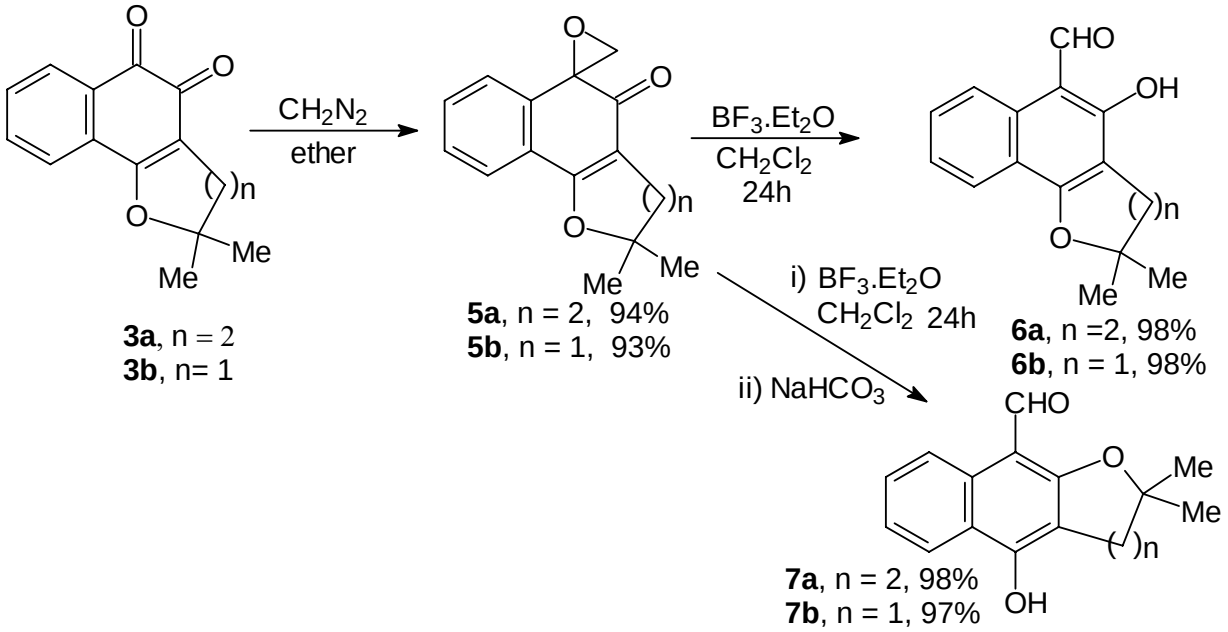
Despite the vast pharmacological studies on β-lapachone **3a**, only a few studies have been addressed to chemical modifications at the redox center. Recently, Burton and coworkers[22] reported the synthesis of monoarylimine *o*-quinones derived from β-lapachone **3a** in an attempt to alter the redox cycling characteristics of the parent molecule. The phenylimine derivatives **3c** or **3d** were found to retain most of the cytotoxicity and selectivity of the β-lapachone **3a** when tested *in vitro* in screen of 55 cancer cell lines. Pinto *et al* also have demonstrated changes in the trypanocidal activities by a select transformation of the *o*-quinone moieties of lapachones. For instance, the introduction of an oxazole nucleus (e.g. **4**) in the β-lapachone (**3a**) structure showed a marked influence upon the trypanocidal activity.[23] In recent studies, we have demonstrated that chemical modification at the redox moiety leads to alterations on some physical chemical properties.[24] Therefore, the search for new compounds by modifying the quinonoid center is a subject of great interest, not only from the chemical but also from the pharmacological points of view.

We wish to report a novel synthetic pathway to prepare **6a-b** and **7a-b** structurally related to β-lapachone **3a** and nor-β- lapachone **3b** (its semi-synthetic lower homolog), respectively, and an investigation of the chemoselective nucleophilic addition at carbonyl C6 of **3a**.

Results and Discussion

The synthetic route for preparing **6a-b** and **7a-b** from β-lapachone **3a** and nor-β- lapachone **3b** is outlined in Scheme 1.

As shown in Scheme 1 the synthesis of **6a-b** and **7a-b** were carried out in two steps. The first involved the preparation of lapachone-epoxide derivatives **5a-b**, which were obtained in high yields from the reaction of lapachones **3a-b** with diazomethane[25] in ether. The reaction of α-lapachone[26,27] and β-lapachone (**3a**) with diazomethane leading to epoxide adducts had been previously described in the literature. Pinto *et al* tested **5a** for blockage of cercaial skin penetration by *Schistosoma mansoni*. The activity of **5a** was found to be 50% lower than those of lapachol (**1**) and β-lapachone (**3a**).



Scheme 1

NMR spectroscopic data for **5a** have not been previously reported and hence have been obtained in this study. NMR spectroscopic techniques, such as ^{1}H X ^{1}H-2D NMR NOESY, clearly confirm that addition of diazomethane to **3a** occurs at the carbonyl C6, e.g., coupling was observed between the hydrogen at C7 (δ = 7.22 ppm) and the hydrogens of the methylene group C11 (δ = 3.11 and 3.44 ppm). A similar observation was found for the addition of diazomethane to **3b**, which produced the new epoxide **5b** in high yield. The chemoselectivities found in the reactions of **3a** and **3b** with diazomethane is not surprising, since there are several reports in the literature indicating that the carbonyl nearest to the aromatic ring is the more reactive.[22,24]

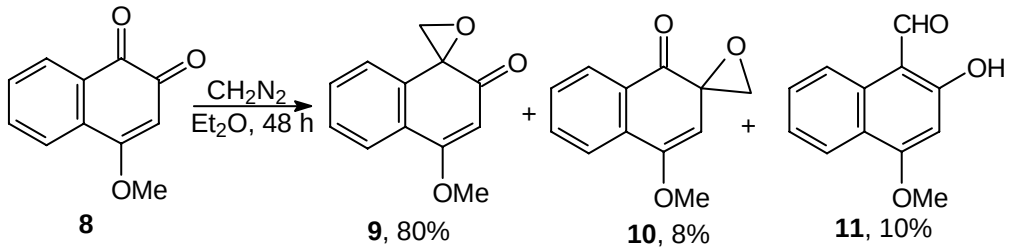
In order to investigate the chemoselectivities of the carbonyls C6 (for **3a**) and C5 (for **3b**) we undertook a full geometry optimization of **3a** and calculation of the geometry parameters for the optimized minima. The *ab initio* calculation was performed using the Gaussian 98W[28] package, with the Lee-Yang-Par[29] correlation functional (B3LYP) and the basis set, 6-311+G(d). Some selected calculated geometry parameters for the optimized minima can be compared, in Table 1, with values obtained from a report of an earlier X-ray structure determination.[30] Both calculated

and observed dihedral angles for the carbonyl indicated that it is almost in the plane of the aromatic system. All calculated geometry parameters are also in good agreement with the values determined in the X-ray study. The difference between the atomic charges for C5 and C6 are small, but they do indicate that C6 is more electrophilic than C5. This difference must account, partially at least, for the greater reactivity of C6 towards nucleophiles.

Table 1. Comparison of selected geometry parameters of the optimized minima for **3a** using B3LYP/6-311+G(d) with values determined by X-ray crystallography

Parameter	Calculated	Determined by X-ray crystallography
Dihedral $O6^{//}$-C6-C5-$O5^{//}$	0.4°	3°
Bond angle C6-C5-$O5^{//}$	119.2°	118.3°
Bond angle C5-C6-$O6^{//}$	119.8°	119.6°
Bond lengths C6-C5	1.523 Å	1.542 Å
Bond lengths C6-$O6^{//}$	1.215 Å	1.210 Å
Bond lengths C5-$O5^{//}$	1.220 Å	1.223 Å
Atomic charge at C5	+0.472	-----
Atomic charge at C6	+0.484	-----

In order to obtain information about the role of the pyran ring in the chemoselectivity of the carbonyls C6(for **3a**) and C5 (for **3b),** the addition of diazomethane to 4-methoxy-1,2-naphthoquinone (**8**) was studied (Scheme 2). The reaction was not chemoselective as shown in reaction 1, where both epoxides **9** (80% yield) and **10** (8% yield), as well as **11** were produced. The formation of **10** in the reaction of **8**, suggests that the chemoselectivity observed in reactions of **3a** and **3b** is partially, at least, due to the steric hindrance of the CH_2 group of the pyran ring towards the incoming diazomethane.



8 **9**, 80% **10**, 8% **11**, 10%

Scheme 2

In the second step of our synthetic route (see Scheme 1), different modes of isomerization of the epoxides **5a-b** to either **6a-b** or **7a-b** could be effected. The reaction of the epoxides with $BF_3.OEt_2$ in dichloromethane proceeded smoothly to give the aldehydes **6a-b** in high yield.

However, the same reaction, but with a basic work up with $NaHCO_3$, led to the isomeric aldehydes **7a-b** also in high yields. It seems that the basic work-up before isolation of the products results isomerization of the aldehydes **6a-b** to the aldehydes **7a-b**. A similar behavior had been described for α and β-lapachone (**3a**), which can be formed from lapachol (**2**) depending of the pH of the medium.

The structure of the aldehydes, **6a-b** and **7a-b,** were investigated by ^{1}H and ^{13}C NMR in such 1D and 2D experiments as $^{1}Hx^{1}H$-COSY and HETCOR ($^{n}J_{CH}$, n=1,2,3). These two set of aldehydes had different chemical shift values for the aldehyde hydrogens but the same molecular weight in the high resolution mass spectra. The multiplicities of the aromatic hydrogens of **6a-b** are similar to those for **5a-b** and also **3a-b**. However, it was not possible to observe NOE between the aldehyde groups and the vicinal aromatic hydrogen in **6a-b**, and so we could not confirm these structures using these techniques.

All doubts about the structures were solved by carrying out an x-ray structure determination of **6a**. Figure 2 shows a view of the molecule with the crystallographic atom numbering scheme. Displacement ellipsoids are drawn at the 30% probability level. All bond lengths and angles are in the expected ranges. As anticipated, an intramolecular hydrogen bond is formed between the phenolic OH group at C5 and the aldehydic oxygen, O3. The conformation of the C10b-C4a-C4-C3-C2-O1 ring, based on the Pucker parameters [Q = 0.48Å, θ = 52.2°, φ = 92.28°] is a half chair with C2 and C3 on opposite sides of the best plane through the near-planar atoms, O1-C10b-C4a-C4.

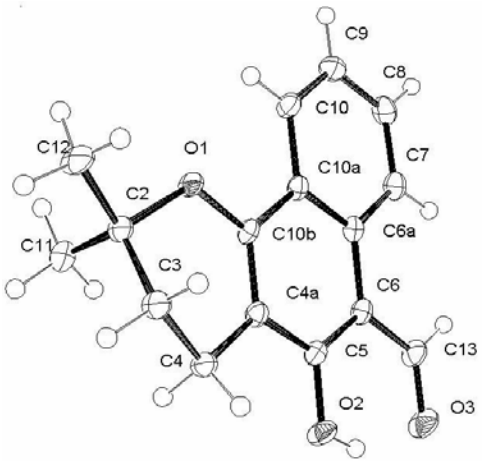


Figure 2

Conclusions

A new method for obtaining aldehyde derivatives of β-lapachone (**3a**) and nor-β-lapachone (**3b**) is reported. The addition of diazomethane to the 1,2-naphthoquinones, (**3a**) and (**3b**), forming the epoxides **5a-b**, occurs chemoselectively at the 1-carbonyl groups. These epoxides can be transformed in high yields to the aldehydes **6a-b or 7a-b** depending on the experimental conditions. To the best of our knowledge, the preparation of **6a-b or 7a-b** represents the first example of the chemoselective formation of aldehyde derivatives in two steps from **3a-b**. *Ab initio* calculations of β-lapachone (**3a**) using B3LYP with basis set 6-311+G* agreed with the carbonyl regiospecifity on forming epoxides, but experimental evidence, obtained from the addition of diazomethane to 1-methoxy-3,4-naphthoquinone (**9**), also suggested an influence from the steric hindrance of the CH_2 group of the pyran ring is also involved in the chemoselectivity. The applicability of the present procedure for the preparation of other naphthoquinone-aldehydes is currently under investigation.

Experimental Section

General Procedures. Melting points were observed on a Reichert micro hotstage and are uncorrected. Analytical grade solvents were used. The solvents were previously purified as described in the literature.[31] Methanol was distilled before being used. Column chromatography was performed on silica gel 60 (Merck 70-230 mesh). Infrared spectra were recorded on a Perkin-Elmer FT-IR Spectrum One spectrophotometer calibrated relative to the 1601.8 cm^{-1} absorbance of polystyrene. Ultraviolet (UV) spectra were obtained on a Schimadizu spectrophotometer: wavelengths in nm and extinction coefficients, ε, in $mol.cm^{-1}$. NMR spectra in $CDCl_3$ solutions were recorded on a Varian Unity Plus VXR (300 MHz) instrument. Low resolution electron-impact mass spectra (70 eV) were measured in a Hewlett Packard 5985 instrument and high-resolution electron-impact mass spectra (70 eV) were obtained using a VG Auto Spec instrument. β-lapachone (**3a**) and nor-β-lapachone (**3b)** were prepared from lapachol by standard procedures[32]. Crystal data of **6a**, space group Pbca**,** were collected on a Nonius KappaCCD diffractometer by the EPSRC X-Ray crystallographic service, based at the University of Southampton, UK. The structure solution and refinement were achieved using SHELX97 and SHELXL97.[33] Full matrix least squares on F^2 converged to R = 0.482 [$I > 2\sigma(I)$]. Atomic coordinates, bond lengths, angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre, deposition number 212908. 6-311+G(d) *Ab initio* calculations were carried out through the Gaussian 98W package running on a PC Pentium III 1.1 GHz.

General procedure for preparing 5a-b

To a solution of the appropriate lapachone in ether was added a ethereal solution of freshly prepared diazomethane. The mixture was kept in the refrigerator (5 ^oC) for 48 hours. After this

time, it was evaporated under reduced to leave a viscous oil, which was purified by column chromatography in silica-gel eluting with a gradient mixture of hexane and ethyl acetate (9/1 to 7/3).

2,3-Dihydro-2,2-dimethyl-spiro-[4*H*-1-oxaphenanthrene-6,2′-oxyran]-5(6*H*)-one (5a). A reaction of 3**a** (1 g, 4.13 mmol) with diazomethane (20 mL) in ether produced the epoxide **5a** (990 mg, 94%) as a slightly yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45, 1.46 (s, 6H, $2CH_3$), 1.80 (1H, m , CH_2), 1.85 (1H, m , CH_2), 2.47 (1H,ddd, *J*= 17.7, 7.2, 6.6, Hz, CH_2), 2.60 (1H, dt, *J* = 17.7, 6.6, Hz, CH_2), 3.11 (d, 1H, *J* = 8.1, Hz, CH_2), 3.44 (d, 1H, *J* = 8.1, Hz, CH_2), 7.22 (1H, ddd, *J* = 7.5, 6.0, 2.1 Hz), 7.40 (1H,td, *J*= 7.5, 2.1 Hz), 7.43 (1H,td, *J* = 7.5, 2.1 Hz), 7.89 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2 (CH_3-C), 26.8 (CH_3-C), 16.1 (CH_2), 31,4 (CH_2), 61.7 (CH_2-O, epoxide), 54.8 (C_6 quaternary), 78.4 (C_2 quaternary), 109.9 (C_{4a} quaternary), 129.6 (C_{6a} quaternary), 136.0 (C_{10a} quaternary), 161.7 (C_{10b} quaternary), 190.9 (C_6, C=O), 122.6 (C_7 Ar), 127.8 (C_8 Ar), 129.9 (C_9 Ar), 123.5 (C_{10} Ar). IR ν_{max}(cm^{-1}, film) 2980 - 2820 (CH_2, CH_3), 1650 (C=O). MS (m/z) (relative intensity %): 256 ($M^{+\cdot}$, 68), 223 (28), 241 (24), 200 (M^+, 100) 200 (100), 115 (22). EI-HRMS (m/z) 256.1099, calcd. for $C_{16}H_{16}O_3$: 256.1099.

2,3-Dihydro-2,2-dimethyl-spiro-[1-oxacyclopent(a)naphthalene-5,2′-oxyran]-5-(4*H*)-one (5b). The reaction of **3b** (1.00 g, 4.38 mmol) with freshly prepared diazomethane (20 mL) in ether produced the epoxide **5b** (990 mg, 93%) a slightly yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59 (s, 6H, $2CH_3$), 2.92 (s, 2H), 3.12 (d, 1H, *J* = 8.1, 7.8 Hz, CH_2), 3.47 (d, 1H, *J* = 8.1, 7.8 Hz, CH_2), 7.25 (1H, ddd, *J* = 7.8, 1.2, 0.9 Hz, Ph-H), 7.42 (1H, td, *J* = 7.2, 1.5 Hz, Ph-H), 7.48 (1H, td, *J* = 7.5, 1.5 Hz, Ph-H), 7.72 (1H, ddd, *J* = 7.5, 1.5, 0.9 Hz, Ph-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2 (CH_3-C), 28.2 (CH_3-C), 39.3 (CH_2), 61.2 (CH_2-O, epoxide), 56.1 (C_5 quaternary), 92.2 (C_2 quaternary), 112.1 (C_{3a} quaternary), 125.6 (C_{5a} quaternary), 138.7 (C_{9a} quaternary), 168.3 (C_{9b} quaternary), 187.7 (C_4, C=O), 123.3 (C_6 Ar), 127.9 (C_7 Ar), 130.9 (C_8 Ar), 124.1 (C_9 Ar). IR ν_{max}(cm^{-1}, film) 2820 - 2980 (C-H), 1650 C=O. EIMS (m/z) (relative intensity %) 242 ($M^{+\cdot}$, 100), 227 (68), 199 (28), 128 (17), 115 (25). EIHRMS (m/z) 242.0945. Calcd. for$C_{15}H_{14}O_3$: 242.0942.

Reaction of 4-methoxy-1,2-naphthoquinone with diazomethane

To a solution of **8** (367 mg, 0.195 mmol) in ether (10 mL) was added a ethereal solution (10 mL) of freshly prepared diazomethane. The mixture was kept in the refrigerator (5 ^{o}C) for 48 hours. After this time, it was evaporated under reduced pressure to leave a viscous oil, which was separated by column chromatography in silica-gel eluting with a gradient mixture of hexane and ethyl acetate (9/1 a 7/3) into to give **9**, **10** and **11**.

4-Methoxy-spiro-[naphthalene-1, 2′-oxyran]-2(1*H*)-one (9). The compound **9** (299 mg, 1.48 mmol) was obtained as an oil in 80% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (s, 3H, O-CH_3), 6.02 (s, 1H, C-H), 7.25 (1H, ddd, *J* = 7.2, 1.8, 0.9 Hz, Ph-H), 7.43 (1H, td, *J* = 7.5, 1.5 Hz, Ph-H), 7.49 (1H, dd, *J* = 7.5, 1.8 Hz, Ph-H), 7.91 (1H, dd, *J* = 7.5, 1.5 Hz, Ph-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.2 (CH_3-O), 105.9 (CH), 57.8 (CH_2-O, epoxide), 169.0 (C_1 quaternary), 132.4

(C_{4a} quaternary), 136.8 (C_{8a} quaternary), 184.5 (C_2, C=O), 122.6 (C_5-Ar), 128.5 (C_6-Ar), 132.5 (C_7-Ar), 126.3 (C_8-Ar). IR ν_{max} (cm^{-1}, film) 2980 (CH), 1750 (C=O). EIMS (m/z) (relative intensity %) 202 ($M^{+\cdot}$, 100), 187 (68), 129 (34), 115 (45), 102 (40). EIHRMS (m/z) 202.0605. Calcd. for $C_{12}H_{10}O_3$: 202.0629.

4-Methoxy-spiro-[naphthalene-2, 2′- oxyran]-1(2*H*)-one (10). The compound **10** (28 mg, 0.15 mmol) was obtained as an oil in 8% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (s, 3H, O-CH_3), 5.85 (s, 1H, C-H), 7.26 (dd, 1H, *J* = 7.5, 1.5 Hz, Ph-H), 7.43 (dd, 1H, *J* = 1.5, 7.5 Hz, Ph-H), 7.49 (dd, 1H, *J* = 1.5, 7.5 HZ, Ph-H), 7.92 (dd, 1H, *J* =1.5, 7.8 Hz, Ph-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.4 (CH_3-O), 101.1 (CH), 62.1 (CH_2-O epoxide), 168.9 (C_1 quaternary), 54.0 (C_3 quaternary) ,132.4 (C_{4a} quaternary), 136.6 (C_{8a} quaternary), 185.6 (C_4, C=O), 123.0 (C_5-Ar), 128.1 (C_6-Ar), 131.1 (C_7-Ar), 124.3 (C_8-Ar). IR ν_{max}(cm^{-1}, film) 2990 (CH), 1760 (C=O). EIMS (m/z) (relative intensity %) 202 (50), 187 ($M^{+\cdot}$ - Me, 100), 129 (40),114 (76), 102 (62). EIHRMS (m/z) 202.0656, Calcd. for$C_{12}H_{10}O_3$: 202.0629.

2-hydroxy-4-methoxy-naphthalene-1-carbaldehyde (11). The aldehyde **11** (37 mg, 0.18 mmol) was obtained as an oil in 10% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.07 (s, 3H, O-CH_3), 6.46 (s, 1H, C-H), 13.84 (1H, s, OH), 10.57 (1H, s, CHO), 7.41 (1H, ddd, *J* = 8.4, 6.9, 1.2 Hz, Ph-H), 7.61 (1H, ddd, *J* = 8.7, 6.9, 1.5 Hz, Ph-H), 8.18 (1H, ddd, *J* = 8.7, 7.2, 1.2 Hz, Ph-H), 8.22 (1H, d, *J* = 8.7 Hz, Ph-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.1 (CH3-O), 96.7 (CH), 168.4 (C_1 quaternary), 163.8 (C_3 hydroxyl group), 105.2 (C_4 quaternary), 130.8 (C_{4a} quaternary), 133.6 (C_{8a} quaternary), 190.7 (C_9, C=O), 123.8 (C_5 -Ar), 129.6 (C_6 -Ar), 123.2 (C_7 -Ar), 118.4 (C_8 -Ar). IR ν_{max}(cm^{-1}, film) 2980 (CH), 1780 (C=O).

General procedure for preparing 6a-b

To solution of the appropriate epoxide in dichloromethane (20mL), externally cooled by ice and under a nitrogen atmosphere, was slowly added an ethereal solution of $BF_3.OEt_2$ The reaction was stirred for 24h at room temperatures and then diluted with dichloromethane (10 mL). To this solution was added anhydrous sodium sulfate (1 g) and activated charcoal (3 g). The mixture was filtered and concentrated under reduced pressure leaving a viscous oil, which was quickly passed through a column chromatography eluting with hexane /ethyl acetate.

5-Hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-benzo[h]chromen-6-carbaldehyde (6a). The aldehyde **6a** (189 mg) was obtained from **3a** (193 mg, 0.75 mmol) and $BF_3.OEt_2$ (0.05 mL) in 98% as brown solid. m.p. 98-100 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51, 1.51(s, 6H, $2CH_3$), 1.94 (2H, t, *J* = 6.6 Hz, CH_2), 2.83 (2H, t, *J*= 6.6 Hz, CH_2), 7.96 (1H d, *J* = 8.1 Hz, Ph-H), 7.49 (1H, t, *J* = 7.5 Hz, Ph-H), 7.65 (1H, t, *J* = 8.1 Hz, Ph-H), 8.16 (1H, d, *J* = 7.8 Hz, Ph-H), 9.13 (1H,s CHO). ^{13}C RMN (75 MHz, $CDCl_3$) δ 26.7 (CH3-C), 26.7 (CH_3-C), 15.8 (CH_2), 31.1 (CH_2), 106.1 (C_6 quaternary), 79.9 (C_2 quaternary), 107.2 (C_{4a} quaternary), 122.3 (C_{6a} quaternary), 130.8 (C_{10a} quaternary), 166.48 (C_{10b} quaternary), 170.6 (C_5 quaternary), 174.1 (CHO), 118.8 (C_7 Ar), 126.1 (C_8 Ar), 131.1 (C_9 Ar), 123.9 (C_{10} Ar). IR ν_{max}(cm^{-1}, film) 3500

(OH), 2820 - 2980 (C-H), 1620 (C=O). EIMS (m/z) (relative intensity %): 256 ($M^{+\cdot}$, 100), 201 (85), 213 (44), 200 (97), 159 (50),115 (52).

2,2-Dimethyl-4-hydroxy-2,3-dihydro-naphtho[1,2-b]furan-5-carbaldehyde (6b). The aldehyde **6b** (990 mg) was obtained from **3b** (1.0 g, 0.5 mmol) and $BF_3.OEt_2$ (0.05 mL) in 98% as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66 (1H, s, 6H, $2CH_3$), 3.19 (s, 2H, CH_2), 7.52 (1H, t, *J* = 7.8 Hz), 7.71 (1H, t, *J* = 7.2 Hz), 7.99 (1H, d, *J* = 7.5 Hz), 8.03 (1H, d, *J* = 7.8 Hz), 9.11(s, 1H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3 (CH_3-C), 28.3 (CH_3-C), 38.5 (CH_2), 110.8 (C_5 quaternary), 95.2 (C_2 quaternary), 108.4 (C_{3a} quaternary), 118.2 (C_{5a} quaternary), 133.8 (C_{9a}

quaternary), 168.1 (C_{9b} quaternary), 172.3 (C_4 quaternary), 173.4 (CHO), 126.3 (C_6 Ar), 132.1 (C_7 Ar), 124.4 (C_8 Ar), 119.6 (C_9 Ar). IR ν_{max}(cm^{-1}, film) 3470 (OH), 2820 - 2980 (CH), 1620 (C=O). EIMS (m/z) (relative intensity %) 242 ($M^{+\cdot}$, 86), 227 ($M^{+\cdot}$ - Me, 100), 110 (8). EIHRMS (m/z) 242.0956. Calcd. for$C_{15}H_{14}O_3$: 242.0942.

General procedure for preparing 7a-b

To solution of the appropriate epoxide in dichloromethane (20mL), externally cooled by ice and under nitrogen atmosphere, was slowly added an ethereal solution of $BF_3.OEt_2$ The reaction was stirred for 24 at room temperatures an then diluted with dichloromethane (10 mL). To this solution was added a saturated solution of sodium bicarbonate (10 mL). After stirring for 1h, the organic phase was separated, extracted with water (2x10mL), dried over anhydrous sodium sulfate and, concentrated under reduced pressure, leaving a viscous oil, which was quickly passed through a column chromatography eluting with hexane /ethyl acetate.

5-Hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*H*]chromen-6-carbaldehyde (7a). The aldehyde **7a** (108 mg) was obtained from **3a** (110 mg, 0.43 mmol) and $BF_3.OEt_2$ (0.05 mL) in 98% as a red viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43, 1.46 (s, 6H, $2CH_3$), 1.87 (2H, t, *J* = 6.6 Hz, CH_2), 2.75 (2H, t, *J* = 6.9 Hz, CH_2), 7.49 (1H, dd, *J* = 8.4, 1.2 Hz, Ph-H), 7.33 (1H, t, *J* = 7.5 Hz, Ph-H), 8.13 (1H, d, *J* = 6.9 Hz, Ph-H), 8.15 (1H, d, *J* = 8.4 Hz, Ph-H), 14.20 (1H, s, OH), 10.54 (1H, s, CHO). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6 (CH_3-C), 26.6 (CH_3-C), 16.1 (CH_2), 31.4 (CH_2), 106.1 (C_{10} quaternary), 76.8 (C_2 quaternary), 105.4 (C_{4a} quaternary), 132.3 (C_{9a} quaternary), 120.6 (C_{5a} quaternary), 157.7 (C_{10a} quaternary), 166.4 (C_5- OH), 190.1 (CHO), 128.5 (C_9 Ar), 123.4 (C_8 Ar), 117.9 (C_7 Ar), 122.7 (C_6 Ar). IR ν_{max}(cm^{-1}, film) 3500 (OH), 2820 - 2980 (CH), 1620 (C=O). EIMS (m/z) (relative intensity %): 256 ($M^{+\cdot}$, 98), 200 (100), 213 (48), 201 (89), 115 (43). EIHRMS (m/z) 256.1099. Calcd. for$C_{16}H_{16}O_3$: 256.1099.

4-Hydroxy-2,2-dimethyl-2,3-dihydo-naphtho[2,3-*b*]furan-9-carbaldehyde (7b). The aldehyde **7b** (47 mg) was obtained from **3b** (50 mg, 0.21 mmol) and $BF_3.OEt_2$ (0.05 mL) in 97% as a red viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (s, 6H, $2CH_3$), 3.16 (2H, s, CH_2), 7.37 (1H, td, *J* = 7.8, 0.9 Hz), 7,57 (1H, td, *J* = 8.7, 1.5 Hz), 7.95 (1H, dd, *J* = 8.1, 1.2 Hz), 8.24 (1H, d, *J* = 8.7 Hz), 13.94 (1H, s, OH), 10.54 (1H, s , CHO). ^{13}C NMR (75 MHz, CDCl3) δ 28.4

(CH_3-C), 28.4 (CH_3-C), 39.4 (CH_2), 106.8 (C_9 quaternary), 91.2 (C_2 quaternary), 109.5 (C_{3a} quaternary), 134.8 (C_{8a} quaternary), 116.4 (C_{4a} quaternary), 164.8 (C_{9a} quaternary), 163.9 (C_4 , OH), 190.0 (CHO), 129.2 (C_8 Ar), 123.4 (C_7 Ar), 118.7 (C_6 Ar), 123.2 (C_5 Ar). IR ν_{max}(cm^{-1}, film) 3458 cm-1 (OH), 2820 - 2980 (CH), 1620 (C=O). EIMS (m/z) (relative intensity %) 227 ($M^{+\cdot}$ - Me 100), 171 (23), 149 (28), 115 (25) 69(59). EIHRMS (m/z) 242.0917. Calcd. for$C_{15}H_{14}O_3$: 242.0942.

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References

1. Santos A.F.; Ferraz, P.A.L.; Pinto, A.V.; Pinto, M.C.F.R.; Goulart, M.O. F.; Sant'Ana, A.E.G. *Int. J. Parasitol.* **2000**, *30*, 1199. dos Santos, A.F.; Ferraz, P.A.L.; de Abreu, F.C.; Chiari, E.; Goulart, M.D.F.; Sant'Ana, A.E.G. *Planta Med.* **2001**, 67, 92.
2. Teixeira, M.J.; Almeida, Y.M.; Viana, J.R.; Holanda Filha, J.G.; Rodrigues, T.P.; Prata, J.R.C. Jr.; Coelho, I.C.B.; Rao, V.S. Pompeu, M.M. L. *Phytoterapy Res.* **2001**, *15*, 44.
3. Almeida E.R. *J. Ethnopharmacol.* **1990**, *29*, 239.
4. Garnier, S.; Wolfender, J.-L.; Nianga, M. Stoeckli-Evans, H.; Hostettmann, K. *Phytochemistry* **1996**, *42*, 1315.
5. Weaver, R.J; Dickins, M.; Burke, M.D. *Biochem. Pharmacol.* **1993**, *46*, 1183.
6. Knecht, W.; Henseling, J.; Löffler, M. *Chem.-Biol. Interac.* **2000**, *124*, 61.
7. Carvalho, L.H.; Rocha, E. M.M.; Raslan, D.S.; Oliveira, A.B.; Krettli, A.U. *J. Med. Biol. Res.* **1988**, *21,* 485.
8. Santos A.F.; Ferraz, P.A.L.; Pinto, A.V.; Pinto, M.C.F.R.; Goulart, M.O.F.; Sant'Ana, A.E.G. *Int. J. Parasitol.* **2000**, *30*, 1199. dos Santos, A.F.; Ferraz, P.A.L.; de Abreu, F.C.; Chiari, E.; Goulart, M.D.F.; Sant'Ana, A.E.G. *Planta Med.* **2001**, 67, 92.
9. Austin, F.G. *Am. J. Trop. Med. Hyg.* **1974**, *23*, 412. Pinto, A.V.; Pinto, M.C.R.; Gilbert, B.; Pellegrino, J.; Mello, R.T. *Trans Roy. Soc. Trop. Med. Hyg.* **1977**, *71*, 133.
10. Kumagai, Y.; Tsurutani, Y.; Shinyashiki, M.; Takeda, S.H.; Nakai, Y.; Yoskikawa, T.; Shimojo, N. *Environ. Toxicol. Pharmacol.* **1997**, *3*, 245.

11. Molina Portela, M.P.; Fernandez Villamil, S.H.; Perissinotti, L.J.; Stoppani, A. O. *Biochem. Pharmacol.* **1996**, *52*, 1875.
12. Beckman, K. B.; Ames, B. N. *J. Biol. Chem.* **1997**, *272*, 19633.
13. Li, J.C.; Wang, C.; Pardee B.A. *Cancer Res.* **1995**, *55*, 3712.
14. Pardee, A. B.; Li, Y. Z.; Li, C. J. *Curr. Cancer Drug Targets* **2002**, *2*, 227.
15. Huang, L.; Pardee, A.B. *Mol. Med.* **1999**, *5*, 711.
16. Chiang, J.; Averboukh, L.; Pardee A.B. *J. Biol. Chem.* **1993**, *268*, 22463.
17. Frydman, B.; Marton, L.J.; Sun, S.J.; Neder, K.; Witiak, T.D.; Liu, A. A; Wang, H.M.; Mao,Y.; Wu, H.Y.; Sanders, M.M.; Liu, L.F. *Cancer Res.* **1997**, *57*, 620.
18. Li, C. J.; Li, Y.-Z.; Pinto, A. V.; Pardee, A. B.; *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 13369.
19. Boothman, D. A.; Greer, S.; Pardee, A. B. *Cancer Res.* 1987, *47*, 5361. Lamond, J. P.; Kirwin, R.; Wall, M. E.; Boothman, D. A. *Proc. Annu. Meet. Am. Assoc. Cancer. Res.* 1995, 36, A2630.
20. (a) Boothman, D. A.; Greer, S.; Pardee, A. B.; *Cancer Res*. **1987**, *47*, 5361. (b) Boothman, D. A.; Trask, D. K.; Pardee, A. B. *Cancer Res*. **1989**, *49*, 605.
21. Dubin, M.; Fernadez Villamil, S. H.; Stoppani, A. O. *Medicina* **2001**, *61*, 343.
22. Di Chenna, P.H.; Benedetti-Doctorovich, V.; Baggio, R.F.; Garland, M.T.; Burton, G. *J. Med. Chem.* **2001**, *44*, 2486.
23. (a) De Moura, K.C.G.; Emery, F. S.; Neves-Pinto, C.; Pinto, M.C.F.R.; Dantas, A.P.; Salomão, K.; de Castro, S.L.; Pinto, A.V. T. *J. Braz. Chem. Soc.* **2001**, *12*, 325. (b)Neves-Pinto, C.; Malta, V.R. S.; Pinto, M.C.F.R.; Santos, R.H.A.; de Castro, S.L.; Pinto, A.V.A. *J. Med. Chem.* **2002**, *45*, 2112.
24. Carvalho, C.E.M., Ferreira, V.F., Pinto, A.V.; Pinto, M.C.F.R., Harrison, W. *Dyes and Pigments* **2002**, *52*, 209.
25. Antkowiak, W.Z.; Sobczak, A. *Tetrahedron* **2001**, 57, 2799.
26. Ferreira, V.F.; Pinto, A.V.; Pinto, M.C.R.F.; da Silva, M.N.; Skakle, J.M.S.; de Souza, M.C.B.V.; Wardell, S.M.S.V. *Acta Cryst*. **2002**, *C58*, 560.
27. Pinto, A.V.; Pinto, M.C.R.F.; Gilbert, B.; Pellegrino, J.; Mello, R.T. *Trans. Royal Soc. Trop. Med Hyg* **1977**, *71*, 133.

28. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 1998.
29. Lee, C.; Yang, W.; Parr, R.G. *Phys. Rev.* **1988**, *37*, 785.
30. Pereira, M.A., PhD thesis, Universidade de São Paulo, São Carlos, 1989.
31. Ferreira, V.F. *Quim. Nova* **1992**, *15*, 348.
32. Hooker, S. C, *J. Chem. Soc. 1892*, 611.
33. Sheldrick, G.M. *SHELXS*97 and *SHELXL*97, University of Göttingen, Germany, 1997.