SYNTHESIS OF 3,4-DIHYDRO-4-HYDROXY-2,2-DIMETHYL--2*H*--1-BENZOPYRAN-5,8-DIONE. A POTENTIAL KEY INTERMEDIATE FOR THE PREPARATION OF NAPHTHO[2,3-b]PYRANOQUINONES.

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ABSTRACT :The synthesis of pyranoquinone **6** and its application to the elaboration of pyranonaphthoquinone **1b** is described.

The interesting biological properties of naturally occurring naphtho[2,3-b]pyranoquinones[1] have stimulated the synthesis of this class of compounds. The alkylation of 2-hydroxy-1,4-naphthoquinones followed by cyclization has been the most commonly used approach to obtain pyranonaphthoquinones.[2] Recently, two new methods have been described, and both use a carbohydrate derived pyran to assemble the tricyclic system.[3]

As part of a program concerned with the search for new synthetic routes to pyranoquinones, we have recently described a convenient synthesis of 2-acetonylpyranonaphthoquinones.[4] We have now considered that the Diels-Alder cycloaddition of dienes to a pyrano-*p*-benzoquinone such as **6** could be a more flexible route to prepare pyranonaphthoquinones. Surprisingly the synthesis of naphtho[2,3-b]pyranoquinones using this strategy is not known, probably because little work has been done on the synthesis of pyrano-*p*-benzoquinones.[5] The recent work of Brown[6] on the synthesis of some pyrano-*p*-benzoquinones prompted us to report the synthesis of the quinone **6** and its application to the synthesis of racemic 4-hydroxy-α-lapachone(**1b**).

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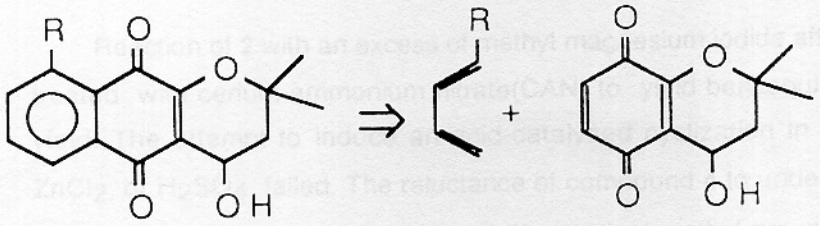
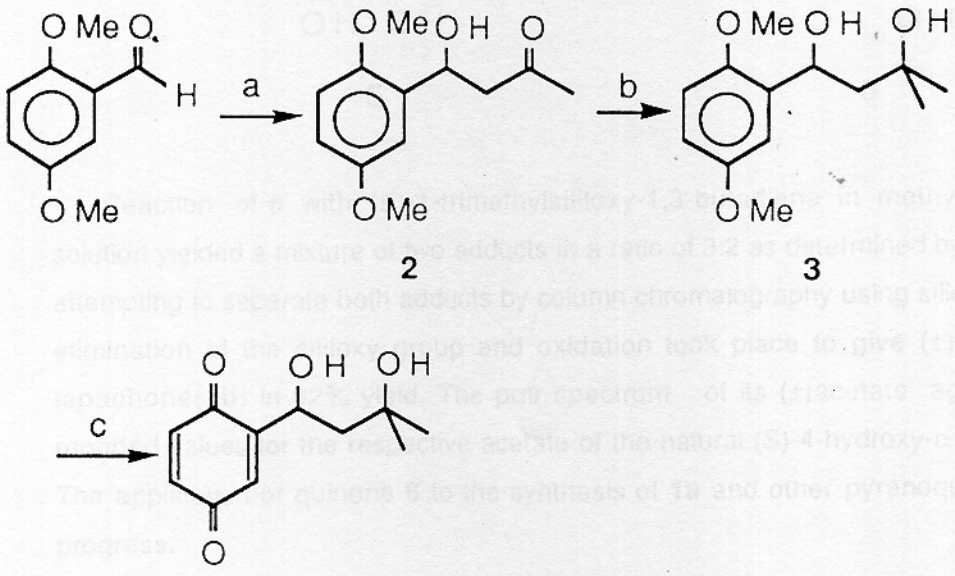


1 a R = OH
b R = H

6

Considering that the nucleophilic addition of alcohols to quinones is quite general it is reasonable to assume a favorable cyclization of the alcohol **4** to the the benzopyrane **6.** In order to explore this synthetic sequence, the preparation of **4**, starting from 2,5-dimethoxybenzaldehyde, was performed as outlined in the following scheme.

It is noteworthy that the reaction of this aldehyde with acetone in the presence of sodium hydroxide affords the corresponding conjugated ketone[7]; nevertheless, using potasium carbonate as base, ketol **2** was obtained in excellent yield.



2

3

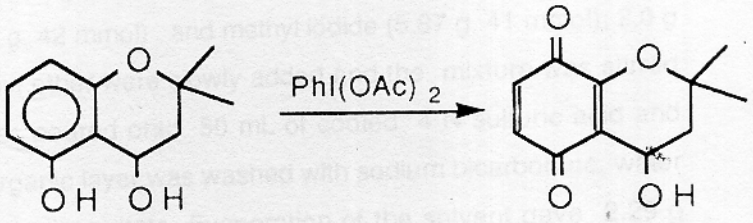
4

a) acetone, K_2CO_3; b) CH_3MgI; c) CAN

SCHEME

Reaction of **2** with an excess of methyl magnesium iodide afforded diol **3**, which was treated with cerium ammonium nitrate(CAN) to yield benzoquinone **4** in 72 % overall yield. The attempt to induce an acid-catalyzed cyclization in **4**, using $BF_3.Et_2O$, or $ZnCl_2$, or H_2SO_4 failed. The reluctance of compound 4 to undergo cyclization probably is due, in part, to the steric effects of the geminal methyl groups toward the C-O bond formation, as has been observed in related intermolecular processes.[8] On the other hand, the acid medium may induce a carbocation character on the C-3' position.

Later we envisaged that an alternative route to **6** could be the oxidation of the known cromanol **5**, obtained in two steps from commercially available 2,6-dihydroxyacetophenone.[9] Thus, oxidation of **5** with iodobenzene diacetate in aqueous acetonitrile afforded the new pyranobenzoquinone **6** in 69% yield.



5 **6**

Reaction of **6** with (E)-1-trimethylsililoxy-1,3-butadiene in methylene chloride solution yielded a mixture of two adducts in a ratio of 3:2 as determined by ^{1}H-NMR. By attempting to separate both adducts by column chromatography using silica gel, a facile elimination of the sililoxy group and oxidation took place to give (±)-4-hydroxy-α-lapachone(**1b**) in 82% yield. The pmr spectrum of its (±)acetate agrees with the reported values for the respective acetate of the natural (S)-4-hydroxy-α-lapachone.[10] The application of quinone **6** to the synthesis of **1a** and other pyranoquinones are in progress.

EXPERIMENTAL

Melting points were determinated with a Kofler modified apparatus and are not corrected. IR spectra were recorded on a Perkin-Elmer Model 1310 Spectrometer. ^{1}H and ^{13}C nmr spectra were recorded on Varian XL-100 and Varian XL-300 spectrometers respectively, using tetramethylsilane as internal reference. Column chromatography was perfomed using Kieselgel 60 (70-230 mesh) . Elemental analyses of all new compounds were performed at the Instituto de Química Orgánica General, Madrid, Spain.

4-(2,5-Dimethoxyphenyl)-4-hydroxy-2-butanone (2).

A mixture of 2,5-dimethoxybenzaldehyde (2.53 g, 15.2 mmol), acetone (5 mL) and potasium carbonate (4 g) was stirred for 5 days at room temperature. The mixture was diluted with 100 mL of water and extracted with ether. The organic layer was dried and concentrated under vacumm to give 3.30 g (97%) of ketol **2** as an oily liquid . IR ν max : 3450 (OH), 1700 (C=O) cm^{-1}. ^{1}H-nmr δ: 2.16 (s, 3H, CH_3CO), 2.6-3.1 (m, 2H, CH_2), 3.78 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3) 5.36 (dd, *J* = 8 and 4 Hz, 1H, CH), 6.76 (m, 2H, ArH), 7.06 (m, 1H, ArH) ppm.

1-(2,5-Dimethoxyphenyl)-3-methyl-1,3-butanediol (3)

To a stirred solution of methyl magnesium iodide in anhydrous ethyl ether (40 mL) , prepared from magnesium (1.02 g, 42 mmol) and methyl iodide (5.87 g, 41 mmol); 2.0 g (10.3 mmol) of **2** in 10 mL of ethyl ether were slowly added and the mixture was stirred for 2 h. The reaction mixture was poured onto 50 mL of cooled 4 N sulfuric acid and extracted with ethyl ether. The organic layer was washed with sodium bicarbonate, water and dried with anhydrous magnesium sulfate. Evaporation of the solvent gave 2.29 g (93%) of diol **3** , m.p. 82-83 °C (from pet. ether 60-80). IR ν max : 3260 (OH) cm^{-1}. ^{1}H-nmr δ: 1.25 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.6-2.1 (m, 2H, CH_2), 3.48 (s, 2H, 2 x OH), 3.76 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 5.33 (dd, *J* = 9 and 4 Hz, 1H, CH), 6.6-6.7 (m, 2H, ArH), 7.0-7.1 (m, 2H, ArH) ppm. ^{13}C-nmr δ: 27.8, 31.7, 48.4, 55.7, 55.8, 67.9, 71.5, 111.4, 112.4, 112.7, 135.8, 150.0, 154.0 ppm.

2-(1,3-Dihydroxy-3-methylbutyl)-2,5-cyclohexadien-1,4-dione (4).

To a cooled solution of diol **3** (0,40 g ,1.67 mmol) in 4 mL of acetonitrile, 2.75 g (5.0 mmol) of CAN in 6 mL of water was added. The mixture was stirred for 30 min at 0 °C , diluted with water and extracted with chloroform. The organic layer were evaporated to yield 0.28 g (80 %) of quinone **4**, after purification by column chromatography (chloroform-ethyl acetate 1:1). I R ν max :3400 (OH), 1645 and 1650 (C=O quinon) cm^{-1}. ^{1}H-nmr δ:1.32 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.5-2.0 (m, 2H, CH_2), 3.1 (s, 1H,OH), 4.78 (s, 1H, OH), 5.0-5.2 (m, 1H, CH), 6.7-6.8 (m, 2H, H-5 and H-6), 6.9-7.1 (m, 1H, H-4) ppm.

3,4-dihydro-4-hydroxy-2,2-dimethyl-2H-1-benzopiran-5,8-dione (6)

To a stirred solution of chromanol **5** (0.15 g, 0.77 mmol) in a mixture of acetonitrile-water (2 :1, v/v 4.5 mL) 0.49 g (1.54 mmol) of iodobenzene diacetate were added. After 15 min the mixture was diluted with water and extracted with chloroform. Evaporation of the solvent and purification of the residue through column chromatography (chloroform) gave 0.11 g (69 %) of pyranobenzoquinone **6**. IR ν max : 3500 (OH), 1660 and 1620 (C=O) cm^{-1}. ^{1}H-nmr δ: 1.42 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 2.04 (ddd, , J = 14.3 and 6.3 Hz, 2H, CH_2), 3.42 (s ,1H, OH), 4.84 (t, J = 6.3 Hz,1H, CH), 6.68 (s, 2H, quinon.) ppm. ^{13}C-nmr δ: 26.6, 26.8, 39.5, 59.0, 79.5, 118.2, 134.3, 136.8, 151.9 181.7, 188.0 ppm.

Reaction of 6 with 1-trimethylsilyloxy-1,3-butadiene.

To a solution of **6** (0.11 g, 0.52 mmol) in 5 mL of dichloromethane was added dropwise 1-trimethylsilyloxy-1,3-butadiene (0.14 g, 1.04 mmol) and the mixture was left for 24 h at room temperature. Evaporation of the solvent gave 0.169 g (91%) of a mixture of adducts in a 3:2 ratio. IR ν max : 3400 (OH), 1680 and 1650 (C=O) cm^{-1}. ^{1}H-nmr δ: 0.03(s, 3.6 H, $SiMe_3$), 0.07 (s, 5.4 H, $SiMe_3$), 1.45 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.7-2.3 (m, 2H, CH_2), 3.0-3.3 (m, 4H, H-6 or H-9, H-5a, H-9a), 4.30-4.5 (m,1H, H-9 or H-6), 4.7-4.9 (m,1H, CH), 5.83 (s, 2H, H-7 and H-8) ppm.

The mixture was purified by column chromatography (15% ethyl acetate- light petroleum as eluent) to give 112 mg (90%) of quinone **1 b** as a yellow oil. IR ν max : 3500, 1685, 1630 cm^{-1}. ^{1}H-nmr δ: 1.50 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 2.14(ddd,J = 14.3 and 6.3 Hz, 2H, CH_2), 3.86 (s, 1H, OH) 5.03 (t,J = 6.3 Hz, 1H, H-4), 7.7-7.9 (m, 2H ArH), 8.1-8.2 (m, 2H ArH). Acetate, yellow crystals, m.p. 138.5-139.5 °C; ^{1}H-nmr δ: 1.51 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.16 (ddd, J = 15.0, 5.0 and 3.0 Hz, 2H, CH_2), 6.10 (dd, J = 5.0 and 3.0 Hz, 1H, H-4), 7.7-7.8 (m, 2H ArH), 8.1-8.2 (m, 2H ArH).

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