SYNTHESIS OF 2*H*-1-BENZOPYRANS FROM ARYLLITHIUM AND α,β-UNSATURATED ALDEHYDES§

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Abstract- The synthesis of 2,2-dialkyl-2*H*-1-benzopyrans **(23)**, **(25)**, **(27)**, **(30)**, **(31)** and **(29)** was performed employing the 1,2-addition reaction of aryllithium salts to cyclocitral, 3-methyl-2-butenal, citral and farnesal respectively. Subsequent deprotection with a Mexican bentonitic earth (Tonsil) in wet acetone was followed by ring closure reaction as the key step. Interesting intermediate products were isolated in the formation of benzopyrans **(30)** and **(31)**.

Intensive interest in the synthesis of 2*H*-1-benzopyrans is due mainly to its occurrence in many biologically active natural products.[1-4] These compounds are considered to be antidepressants,[5] antihypertensive,[6] hypoglycemic[7] along with other properties related to the Mexican folk medicine.[8] Due to their importance, several methodologies have been developed for their preparation; among them the use of a wide range of condensation reactions, thermal rearrangements and ylide reactions.[9] On the other hand, the synthesis of heterocyclic compounds involving aromatic lithiation reactions as key step is a well known process,[10] however few 2,2-dialkyl-2*H*-1-benzopyrans have been synthesized using this method.[11] In the present work we describe the synthesis of some 2,2-dialkyl-2*H*-1-benzopyrans along with other interesting products by utilizing the 1,2-addition reaction of an appropriately protected aryllithium compound (A) to an α,β-

§Dedicated with much admiration and respect to Professor A. R. Katritzky on the occasion of his 65th birthday.

unsaturated aldehyde, and subsequent deprotection and cyclization of the produced carbinol (B) as key step, (Figure 1). This approach mimics the process by which is believed benzopyran rings are formed in nature.[12]

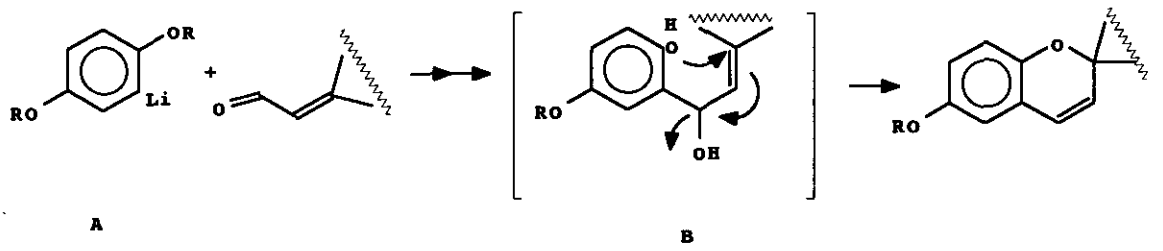
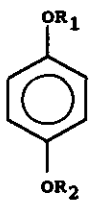


Figure 1

The synthesis of the benzopyrans was carried out as follows. In order to find the more suitable protecting group for lithium salts of type **A**, we prepared several derivatives (**1-8**) by treatment of hydroquinone with the appropriate reagent. The aromatic lithiation reaction was carried out by treatment of the corresponding aromatic ethers (**2-8**) with n-butyllithium in anhydrous ether at room temperature. The lithiation reaction was performed within 3 h in all cases except for **4**, for which after 24 h no metalation was observed. The best results in terms of yield, reaction time and reactivity were observed with compounds which had at least one MOM or THP moiety as protecting group. Furthermore remarkable regioselectivity in the metalation process for the ethers (**6**), (**7**) and (**8**) was observed. In view of the results described above, **2** was chosen to try the addition reaction on different α,β-unsaturated carbonyl compounds. The lithium salt from **2** was reacted with cyclocitral at room temperature under nitrogen atmosphere to give alcohol (**9**) in 64% yield, which was converted into the benzopyran (**23**) in 38% yield by treatment under reflux for 1 h with acetic acid and traces of sulfuric acid. Attempts to convert **9** into **23** under mild conditions[13] afforded in all cases the dehydration product (**17**) in ca. 30% yield.

In order to obtain the benzopyran (**24**) and the natural product (**25**),[14] the lithium salts from **2** and **8** were treated with 3-methyl-2-butenal in the same conditions described above to give the corresponding alcohols (**10**) and (**11**) in 94% and 63% yields, respectively. Attempts to cleave the MOM and THP protection under various reaction conditions[15] gave only polymeric resins. When **10** was treated with Tonsil, a commercially available Mexican bentonitic earth[16] in acetone at room temperature only the corresponding dehydration product (**18**) was obtained in 69% yield. Further attempts to obtain **24** and **25** from **10** and **11** proved futile,



1.- R_1= MOM, R_2=H

2.- R_1= R_2=MOM

3.- R_1= R_2=MTM

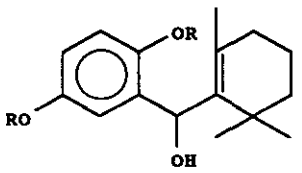
4.- R_1= R_2=MEM

5.- R_1= R_2=THP

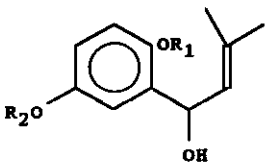
6.- R_1= MOM, R_2=CH_2Ph

7.- R_1= MOM, R_2=Me

8.- R_1= THP, R_2=Me

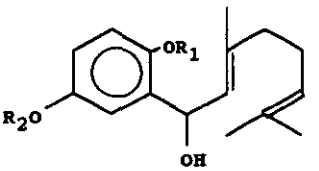


9.- R=MOM



10.- R_1=R_2=MOM

11.- R_1=THP, R_2=Me

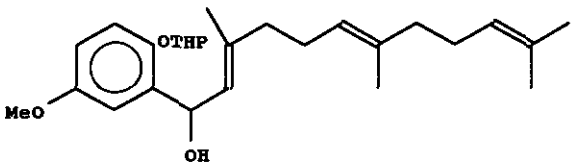


12.- R_1=R_2=MOM

13.- R_1=R_2=THP

14.- R_1=MOM, R_2=Me

15.- R_1=THP, R_2=Me



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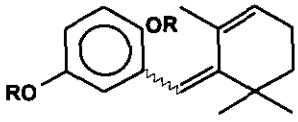
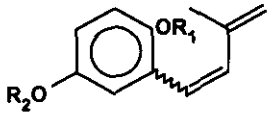
however we were able to obtain the natural product (**25**) in 64% yield by treatment of **11** with Tonsil in wet-acetone.

The two natural products cordiachromen (**26**) and dictyochromenol (**28**) are structurally related compounds to **24** and **25**. The former compound was isolated from *Cordia alliodora,*[17] a native tropical american tree and the later from the brown alga *Dictyopterins undulata* among other piscicidal compounds[2] and its synthesis was reported in the same work in 11% yield. We envisaged that their synthesis could be carried out using the method described above.

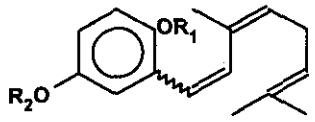
So, in a different set of experiments, the lithium salts from **2, 5, 7** and **8**, were treated with citral in anhydrous THF at room temperature under nitrogen atmosphere to give the corresponding alcohols (**12-15**) in good yields (84, 94, 87 and 95% respectively). In order to obtain cordiachromen (**26**), the alcohol (**12**) was treated under various reaction conditions, however the only product characterized and isolated in good yield (75-85%) was the polyene (**19**). When **12** was treated under more severe acidic conditions, i.e. CF_3CO_2H/CH_2Cl_2, 25°C for 24 h the monocyclization product (**21**) was obtained in 26% yield. Finally



17.- R=MOM

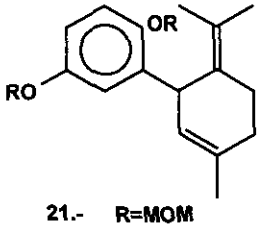


18.- R_1=R_2=MOM

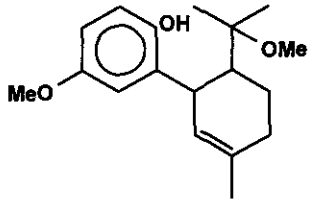


19.- R_1=R_2=MOM

20.- R_1=MOM, R_2=Me



21.- R=MOM



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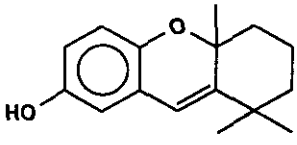

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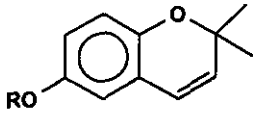
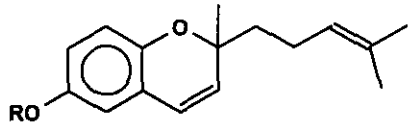


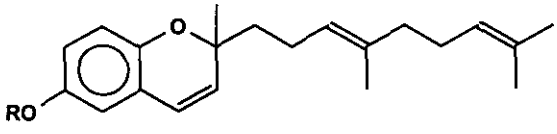
24.- R=H

25.- R=Me



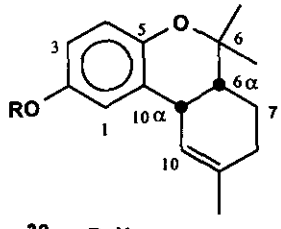
26.- R=H

27.- R=Me



28.- R=H

29.- R=Me



30.- R=H

31.- R=Me

when **12** or **13** was reacted with a solution of 6N HCl in THF under reflux for 1 h or a 50% solution of acetic acid with traces of H_2SO_4 the benzopyran (**30**) was formed in ca. 84% and ca. 60% yield respectively. The same product (**30**) was obtained when **13** was treated with Tonsil and dry acetone at 25°C. The stereochemistry for benzopyran (**30**) was assigned on the basis of its ^{1}H-nmr spectrum and surprisingly the *cis* stereoisomer was the only one detected. The ^{1}H-nmr spectrum of **30** shows signals for three methyl groups (δ 1.25; 1.40 and 1.68 ppm, two aliphatic and one vinylic respectively), two alkyl protons (1.52 ppm, m); a broad signal due to an allylic-CH_2-group at 1.93 ppm and H-6α at 1.96 ppm,[18] a benzylic-allyllic proton (3.45 ppm, m), a exchangeable proton with D_2O at 4.52 ppm, a vinylic proton (5.82 ppm, m) and three aromatic protons (6.75-6.93 ppm, m). Spin decoupling experiments confirmed the AMX spin pattern for the H-6α, H-10α and H-10 (vinylic) protons. Indeed, on irradition of the multiplet at δ 1.60-2.10 ppm, the signals due to H-10 and H-10α were simplified to a doublet J=7 Hz (AB system). When the vinylic proton at δ 5.82 ppm was irradiated, the signal due to H-10α was simplified to a broad doublet J=7 Hz. Finally, when H-10α was irradiated the signal due to H-10 appeared as a broad singlet confirming the allylic relationship of the C-9 methyl group with H-10. The coupling constant between H-6α and H-10α (J=7 Hz) indicates that the dihedral angle between these protons is ca. 40°. Such an angle is only possible if the A/B rings are *cis* fused. Furthermore, the chemical shift of the three methyl groups (at δ 1.25, 1.42 and 1.68 ppm) of **30** was compared with published data[19] where the *cis* (δ 1.24, 1.42 and 1.68 ppm) and *trans* (δ 1.08, 1.38, 1.65 ppm) Δ^9-tetrahydrocannabinol were reliably differentiated. Such observations are consistent with the *cis* structure proposed for **30**.

Additional experiments were carried out, so the treatment of **14** with a solution of hydrochloric acid in acetone or THF lead to the dehydration product (**20**) in 60% yield. When methanol was used as co-solvent in the same reaction, the monocyclic product (**22**) was obtained in 33% yield. Furthermore when **12** and **14** were allowed to react with a solution of HCl in anhydrous THF under carefully controlled reaction time, only the dehydration products (**19**) and (**20**) were isolated, however under prolonged acid treatment of **19** and **21** or **20** and **22** lead to the benzopyrans (**30**) and (**31**) respectively. Moreover, the treatment of alcohols (**13**) and (**15**) with acids led again to the benzopyans (**30**) and (**31**).

In view of the results described above a possible explanation for the formation of the products would be given. The reaction presumably proceeds *via* the formation of a very stable benzylic-allylic carbonium ion as first step (**A**, Figure 2). The formation rate of carbocation **A** may be faster than the hydrolysis rate for the intermediates with different protective groups (R). Like a classical carbocation ion, **A** can eliminate a proton

to form an alkene **B** (products **17-20**) and/or rearrange to give the carbocation **C**, which in turn can lose a proton to afford a new alkene, (D, product **21**) and/or combine with a nucleophilic molecule MeOH to give **E** (product **22**). As described above, the products **B** and **D**, can be converted into the corresponding benzopyrans (**30**) and (**31**).

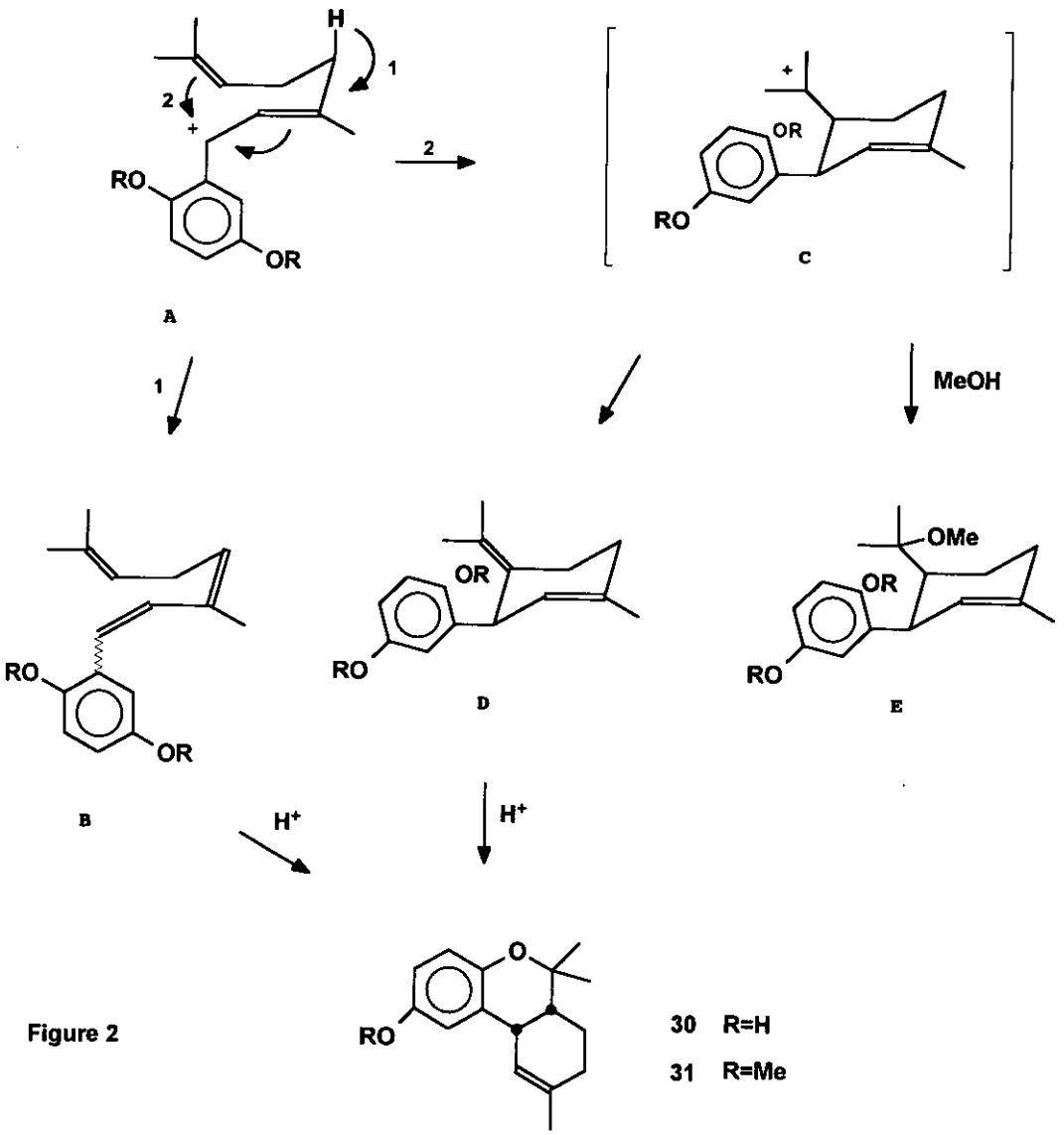
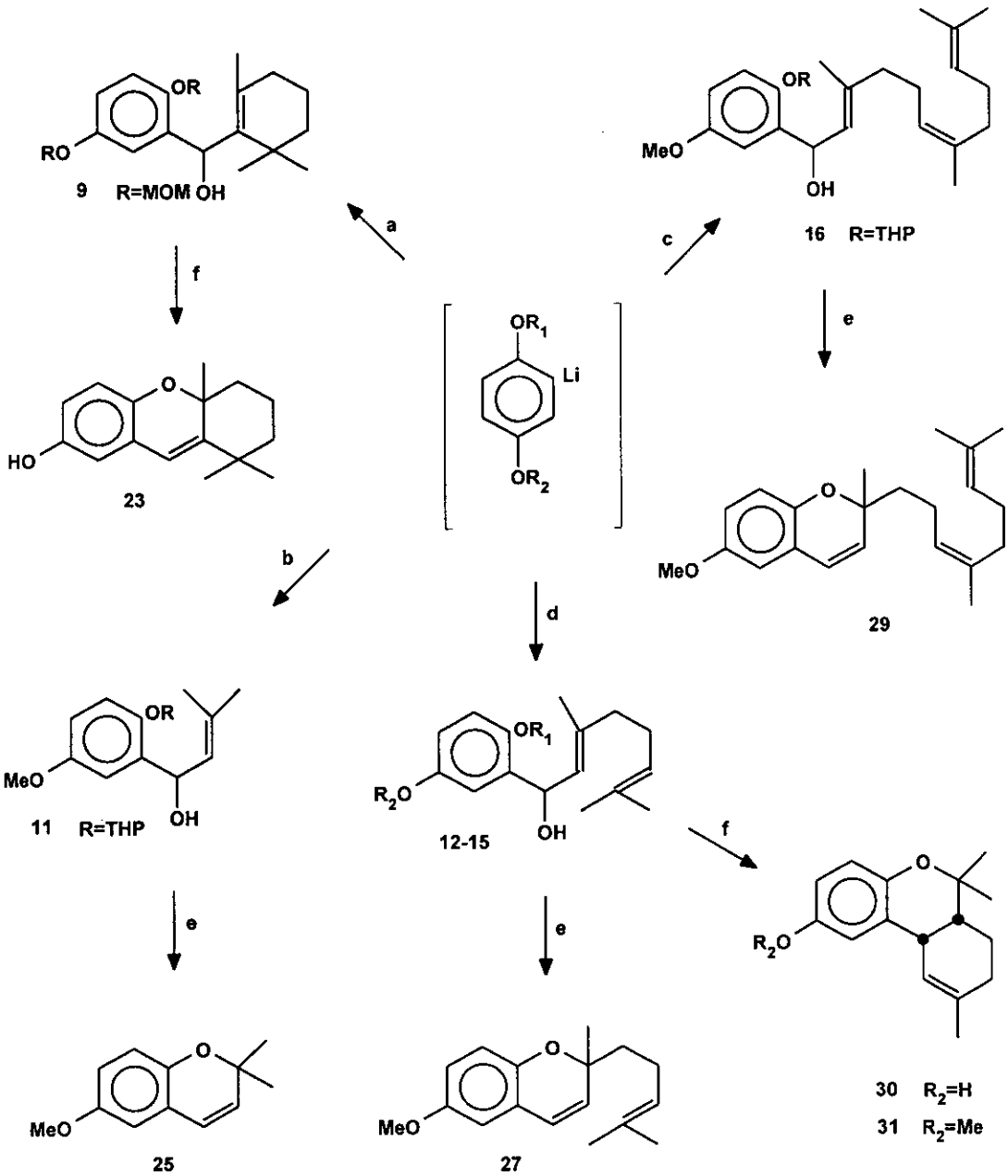


Figure 2

30 R=H

31 R=Me

The 1,2-addition of the lithium salt generated from **8** to farnesal afforded alcohol (**16**) in 62% yield. Acid treatment of **16** led always to untractable mixtures. Finally the syntheses of *O*-methylcordiachromene (**27**), and *O*-methyldictyochromenol (**29**) were accomplished when the alcohols (**15**) and (**16**) were stirred at room



a). Cyclocitral. b). 3-Methyl-2-butenal. c). Farnesal. d). Citral. e). Tonsil / wet acetone. f). TFAA

Scheme 1

temperature with tonsil in wet acetone to afford the benzopyrans (**27**) and (**29**) in 29% and 42% yield respectively.

So far, the results described have shown that the expected benzopyrans (**25**), (**27**) and (**29**) were obtained only when the corresponding alcohols were treated under mild conditions (Tonsil wet acetone) and R_1 = THP and R_2 = Me. These results are summarized in Scheme 1.

Positive results were not obtained with compounds (**3**) and (**6**). In the case of **3** a conventional deprotective method was used[15] affording untractable mixtures and for **6**, the corresponding 1,2-addition reaction went in poor yield.

In summary, we have been able to synthesize the benzopyranes (**23**), (**25**), (**27**), (**29**), (**30**) and (**31**) *via* the 1,2-addition of an aryllithium salt to cyclocitral, 3-methyl-2-butenal citral and farnesal. The best results for the deprotection and subsequent ring closure reaction to give the benzopyrans (**25**), (**27**), (**29**) and (**31**) were obtained when R_1 = THP and R_2 = Me and were carried out under mild conditions (Tonsil wet acetone). On the other hand when acid was used for prolonged time and acid sensitive protecting groups were present in the substrates, the main products were the benzopyrans (**30**) and (**31**).

ACKNOWLEDGEMENTS

We are grateful to the National Science and Technology Council (CONACyT) for a fellowship (No. 51225 to F. P. F.), Drs. M. Romero and J. Cárdenas for their kind discussion and Messrs. R. Gaviño, R. Patiño and L. Velasco for their technical assistance.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. The ir spectra were recorded on a Nicolet FT-5SX spectrophotometer. The ^{1}H-nmr spectra were obtained on a Varian-Gemini 200 and a Varian VXR 300S instruments with TMS as internal standard. Mass spectra were recorded with a Hewlett Packard 5985B spectrometer with gcms system, compounds were introduced through the direct insertion probe.

General procedure for the preparation of MOM, MEM and MTM ethers.

Bis(methoxymethyl)ether of hydroquinone 2.- In a round bottom flask fitted with a magnetic stirrer and nitrogen atomsphere, sodium hydride (1.1 g, 45 mmol) and anhydrous THF (20 ml) were placed and the

system swept with nitrogen. The suspension was cooled to -28°C and a solution of 2 g of hydroquinone (18 mmol) in 30 ml of anhydrous THF was added dropwise via a hypodermic syringe. After stirring for 30 min at room temperature the reaction mixture was again cooled to -20°C and a solution of 3.2 g (40 mmol) of chloromethyl methyl ether was added dropwise via a syringe and the mixture stirred at room temperature. The reaction mixture was conveniently monitored by tlc. After the starting material had disappeared, the solvent was removed under reduced pressure and CH_2Cl_2 was added, cooled with an ice bath and water was added dropwise. The organic layer was separated and the aqueous layer was extracted (2 x 15 ml) with CH_2Cl_2. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by distillation, to give 3.5g (97%) of **2** as an oil, bp 90°C/1 mmHg. (lit.,[20] 75°C/0.3 mmHg). Ir (film) ν_{max} 2897, 1507, 1278, 1152, 1008 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 3.51 (6H ,s), 5.10 (9H, s), 7.01 (4H, s); ms: m/z 198 (M^+, 40.6), 138 (13.5), 45 (100).

Monomethoxymethyl ether of hydroquinone 1. Purified by column chromatography (hexane:acetone 2:1) to afford **1** in 59% yield and **2** in 24% yield. Ir (film) ν_{max} 3380, 3033, 2954, 1510, 1229, 1193, 1151, 1101 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 3.45, (3H, s), 5.25 (2H, s), 6.82 (4H, A_2B_2); ms: m/z 154 (M^+, 17.3), 94 (13.2), 45 (100).

Bis(methylthiomethyl) ether of hydroquinone 3. Anhydrous HMPT was used as solvent, 2 days at room temperature. The product was purified by column chromatography (hexane-ethyl acetate 9:1) to afford **3** in 95% yield. Ir (film) ν_{max} 2919, 1502, 1192, 826 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 2.20 (6H, s), 5.06 (4H, s), 6.87 (4 H, s); ms: m/z 230 (M^+,25), 61 (100).

Bis(methoxyethoxymethyl) ether of hydroquinone 4. Purified by distillation bp 150°C/1mmHg, 88% yield. Ir($CHCl_3$) ν_{max} 2920, 1503, 1220, 1150, 1010 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 3.35 (6H, s), 3.65 (8H, m, A_2B_2), 5.20 (4H, s) 6.95 (4H, s); ms: m/z 286 (M^+,8), 89 (91), 59 (100), 45 (26).

Benzylmethoxymethyl diether of hydroquinone 6. This product was prepared from the monobenzyl ether of hydroquinone in 96% yield. Ir ($CHCl_3$) ν_{max} 3043, 3003, 2956, 2932, 1506, 1193, 1016 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 3.42 (3H, s), 4.95 (2H, s), 5.05 (2H, s), 6.93 (4H, m, A_2B_2); ms: m/z 244 (M^+,23), 91 (97), 45 (100).

Methoxymethylmethyl diether of hydroquinone 7. Prepared in 80% yield from *p*-methoxyphenol as an oil. Ir ($CHCl_3$) ν_{max} 3004, 2985, 1507, 1225, 1150, 1008 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 3.45 (3H, s), 3.75 (3H, s), 5.10 (2H, s), 6.91 (4H, m, A_2B_2); ms: m/z 168 (M^+,15), 123 (39), 45 (100).

Bis(tetrahydropyranyl) ether of hydroquinone 5. In a 100 ml round bottom flask fitted with magnetic stirrer, a solution of 1.5 g (13 mmol) of hydroquinone in 40 ml of ethyl acetate, 3 ml of freshly distilled dihydropyran and a drop of hydrochloric acid was placed and stirred at room temperature overnight. After this time a 2N solution of sodium hydroxide was added. The organic layer was separated and the aqueous layer was extracted with AcOEt (2 x 15 ml). The combined organic layers were washed with water and dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The solid residue was crystallized from hexane to give 3.4 g (89%) of **5** as white crystals. mp 130°C. Ir ($CHCl_3$) ν_{max} 2960, 1500, 1240, 1140, 1060 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.75 (6H, m), 3.75 (4H, m) 5.32 (2H, br), 6.95 (4H, s); ms: m/z 278 (M^+,0.5), 194 (20), 110 (100), 85 (41).

Methyltetrahydropyranyl diether of hydroquinone 8. Prepared in 95% yield from *p*-methoxyphenol and following the procedure for **5**, oil. Ir ($CHCl_3$) ν_{max} 3048, 3005, 2949, 2872, 1508, 1181, 1126, 1074 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.70 (6H, m), 3.75 (3H, s), 3.72 (2H, m), 5.25 (1H, br), 6.85 (4H, m, A_2,B_2); ms: m/z 208 (M^+,4), 124 (100), 109 (35), 85 (31).

General procedure for the metalation and 1,2-addition to α,β-unsaturated aldehydes.

1-[2,5-Bis(methoxymethyloxy)phenyl]-3-methyl-2-buten-1-ol 10. In a three-necked round bottom flask equipped with magnetic stirrer and argon atmosphere a solution of 0.67 g (3.3 mmol) of **2**, in 20 ml of anhydrous ether was placed and a 1.6 M solution of n-buthyllithium in hexane (2 ml, 205 mg, 3.3 mmol) was added and stirred for 2 h at room temperature. After this time, the yellow pale suspension formed was cooled to -10°C and a solution of 0.34 g (4.0 mmol) of freshly distilled 3-methyl-2-butenal in 5 ml of anhydrous ether was added dropwise *via* a hypodermic syringe. The temperature was allowed to rise to 20°C and the reaction mixture was stirred overnight. Ethyl acetate and water were added, the phases were separated and the aqueous layer was extracted (2 x 15 ml) with ethyl acetate. The combined organic layers were washed with water (2 x 15 ml), dried over anhydrous Na_2SO_4 and purified by flash chromatography on silica gel (70-230 mesh) and using a 8:2 mixture of hexane-ethyl acetate as eluent to give 0.895 g (94%) of **10** as an oil. Ir (film) ν_{max} 3500, 2953, 2901, 1605, 1579, 1492, 1152, 1077, 1006 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.72 (3H, d, J=1 Hz), 1.75 (3H, d, J=1 Hz), 2.55 (1H, br, exchangeable with D_2O), 3.45 (6H, s), 5.07 (2H, s), 5.12 (2H, s), 5.35 (1H, dq, J=9 Hz, J=1 Hz), 5.63 (1H, d, J=9 Hz), 6.95 (3H, m). On irradiation of 1.75 ppm frequency the signal at 5.35 ppm was simplified to a doublet J=9 Hz); ms: m/z 282 (M^+,1.5), 220 (5), 205 (53), 45 (100). Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.68; H, 7.71.

1-[2-(2-Tetrahydropyranyloxy)-5-methoxyphenyl]-3-methyl-2-buten-1-ol 11. Prepared in 63% yield, oil, Ir($CHCl_3$) ν_{max} 3443, 2941, 2891, 1608, 1588, 1414, 1190, 1036, 970 cm^{-1}; ^{1}H-nmr (C_6D_6): δ 1.61 (3H, d, J=1 Hz) 1.63 (6H, m), 1.67 (3H, d, J=1 Hz) 2.55 (1H, br, exchangeable with D_2O), 3.42 (3H, s), 3.51 (2H, m), 5.15 (1H, br), 5.67 (1H, dq, J=9 Hz, J=1 Hz), 5.82 (1H, d ,J=9 Hz), 6.18 (1H, dd ,J=8 Hz, J=2 Hz), 7.21 (2H, m); ms m/z 292 (M^+,1) 190 (18), 175 (100), 85 (35). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 69.77; H, 8.12.

1-[2,5-Bis(methoxymethyloxy)phenyl)]-[2,6,6-trimethylcyclohexenyl]carbinol 9. Oil, 64% yield. Ir ($CHCl_3$) ν_{max} 3550, 2920, 1620, 1580, 1480, 1150, 1080, 1000 cm^{-1}; ^{1}H-nmr (C_6D_6): δ 1.10 (3H, s), 1.28 (3H, s), 1.51 (4H, br), 1.91 (3H, s), 2.05 (2H, m), 3.10 (3H, s), 3.15 (3H, s), 3.30 (1H, br), 4.75 (2H, s), 4.85 (2H, s), 5.85 (1H, s), 6.95 (2H, m), 7.35 (1H, m); ms: m/z 350 (M^+, 2), 288 (5), 273 (100, 229 (8). Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.41; H, 8.55.

1-[2,5-Bis(methoxymethyloxy)phenyl]-3,7,dimethyl-2-6-octadien-1-ol 12. Oil, 84% yield. Ir ($CHCl_3$) ν_{max} 3598, 3040, 3007, 2963, 2932, 1665, 1644, 1483, 1191, 1078 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.55 (3H, s), 1.65 (3H, s), 1.75 (3H, d, J=1 Hz), 2.05 (4H, m), 2.10 (1H, br, exchangeable with D_2O), 3.45 (6H, s), 5.07 (2H, s), 5.10 (3H, br), 5.15 (1H, dq, J=9 Hz, J=1 Hz), 5.63 (1H, d, J=9 Hz), 6.95 (3H,m); ms: m/z 350 (M^+,5), 305 (2), 288 (6), 273 (8), 205 (49), 243 (15), 69 (18), 45 (100). Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.32; H, 8.75.

1-[2-(Methoxymethyloxy)-5-methoxyphenyl]-3,7-dimethyl,2,6-octadien-1-ol 14. Prepared in 87% yield. Oil; Ir (film) ν_{max} 3450, 2960, 2920, 1620, 1580, 1490, 1120 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.56 (3H, s), 1.65 (3H, s), 1.75 (3H, d, J=1 Hz), 2.03 (4H, m), 3.45 (3H, s), 3.75 (3H, s), 5.05 (1H, m), 5.11 (2H, s), 5.42 (1H, dq, J=9 Hz, J=1 Hz), 5.65 (1H, d, J=9 Hz), 7.01 (3H, m); ms: m/z 320 (M^+,1.6), 258 (18), 243 (28), 175 (100), 69 (33), 45 (44). Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 70.96; H, 8.72.

1-[2,5-Bis(2-Tetrahydropyranoylxy)phenyl]-3,7-dimethyl-2,6-octadien-1-ol 13. Prepared in 94% yield. Oil; Ir (film) ν_{max} 3430, 2940, 1610, 1580, 1490, 1190, 1030, 1020 cm^{-1}; ^{1}H-nmr (C_6D_6): δ 1.45 (3H, s), 1.51 (3H, s), 1.55 (12H, m), 1.65 (3H, d, J=1 Hz), 2.05 (4H, br), 3.52 (4H, m), 5.22 (2H, m), 5.72 (1H, dq, J=9 Hz, J=1 Hz), 5.95 (1H, d, J=9 Hz), 7.11 (3H, m); ms: m/z 328 (M^+-102,2), 244 (57), 229 (20), 161 (67), 85 (100). Anal. Calcd for $C_{26}H_{38}O_5$: C, 72.52; H, 8.90. Found: C, 72.26; H, 9.07.

1-[2-(2-Tetrahydropyranyloxy)-5-methoxyphenyl]-3,7-dimethyl-2,6-octadien-1-ol 15. Oil, 95% yield. Ir ($CHCl_3$) ν_{max} 3602, 2942, 2864, 1666, 1604, 1493, 1117, 1037, 970 cm^{-1}; ^{1}H-nmr (C_6D_6): δ 1.55 (3H, s), 1.6 (3H, s), 1.75 (3H, d, J=1 Hz), 2.05 (4H, m), 3.45 (3H, s), 4.71 (1H, m), 5.15 (1H, m), 5.70 (1H, dq,

J=9 Hz, J=1 Hz), 5.90 (1H, d, J=9 Hz), 6.72 (1H, dd, J=9 Hz, J=2 Hz) 7.21 (2H, m). Irradiation of the signal at 1.75 ppm simplified the signal at 5.70 to a doublet with J=9 Hz; ms: m/z 360 (M^+,1) 258 (37), 243 (20), 175 (100), 85 (41). Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.51; H, 8.83.

1-[2-(2-Tetrahydropyranyloxy)-5-methoxyphenyl]-3,7,11-trimethyl-2,6,10-undecatrien-1-ol 16. Prepared in 62% yield. Ir ($CHCl_3$) ν_{max} 3600, 3053, 2943, 1666, 1603, 1581, 1493, 1036, 970 cm^{-1}; ^{1}H-nmr (C_6D_6): δ 1.55 (6H, s), 1.62 (3H, s), 1.67 (3H, s), 1.60 (4H, m), 2.05 (8H, br), 3.38 (3H, s), 3.55 (2H, m), 5.15 (3H, m), 5.65 (1H, dq, J=9 Hz, J=1 Hz), 5.93 (1H, d ,J=9 Hz), 6.65 (1H, dd, J=9 Hz, J=1 Hz), 7.21 (2H, m); ms: m/z 326 (M^+-102,8), 311 (5), 175 (100), 151 (50), 137 (15), 85 (53). Anal. Calcd for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 75.72; H, 9.38.

1-[2,5-Bis(methoxymethyloxy)phenyl]-3,7-dimethyl-1,3,6-octatriene 19. To a well stirred solution of 0.45 g (1.3 mmol) of alcohol (**12**) in 15 ml of acetone was added 0.5 ml of conc hydrochloric acid and the mixture was stirred for 30 min at room temperature. After this time the solvent was removed under reduced pressure without heating. The residue was diluted with CH_2Cl_2 and washed with a 10% solution of sodium bicarbonate, water, dried over anhydrous Na_2SO_4 and the solvent was evaporated. The residue was chromatographed on silica gel using a mixture of hexane-ethyl acetate 9:1 as eluent affording **19** (363 mg, 85% yield) as a yellow oil. Ir (film) ν_{max} 3053, 2956, 2928, 1602, 1578, 1491, 1152, 1010 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.70 (9H, br), 2.91 (2H, dd, J=9 Hz, J=9 Hz), 3.51 (6H, s), 5.12 (4H, s), 5.52 (2H, m), 7.10 (5H, m); ms: m/z 332 (M^+,0.1), 198 (10), 136 (20), 69 (100). Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26, H, 8.49. Found: C, 72.41; H, 8.71.

1-[2-(Methoxymethyloxy)-5-methoxyphenyl]-3,7-dimethyl-(1,3,6-octatriene) 20. This compound was prepared by the same procedure described above. Oil, 60% yield, Ir (film) ν_{max} 2980, 2940, 1650, 1630, 1600, 1495, 1200, 1070, 1000 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.72 (9H, br), 2.92 (2H, dd, J=9 Hz, J=9 Hz), 3.45 (3H, s), 3.73 (3H, s), 5.11 (4H, s), 5.52 (2H, m), 7.01 (5H, m); ms: m/z 302 (M^+,20), 257 (5), 201 (27), 69 (18), 45 (100). Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.62; H, 8.53.

3-[2,5-Bis(methoxymethyloxy)phenyl-4-isopropyliden-1-methylcyclohexene 21. To a well stirred solution of 0.5 g (1.42 mmol) of alcohol (**12**) in 15 ml of CH_2Cl_2 was added 1ml of trifluoroacetic acid and the mixture stirred for 12 h at room temperature. After this time, the reaction was monitored by tlc showing several products. An additional 1 ml of acid was added and stirred for further 12 h. After this time the reaction mixture was neutralized with a 10% solution of $NaHCO_3$. The organic layer was washed with water, dried over anhydrous Na_2SO_4 and solvent evaporated under reduced pressure. The product was purified by

column chromatography on silica gel and using hexane-ethyl acetate (95:5) as eluent to give **21** (124 mg, 26%) as an oil. Ir ($CHCl_3$) ν_{max} 2990, 2940, 1650, 1620, 1580, 1490, 1200, 1080 cm^{-1}; ^{1}H-nmr (C_6D_6): δ 1.65 (3H, s), 1.71 (6H, s), 2.15 (4H, m), 3.16 (3H, s), 3.23 (3H, s), 4.21 (1H, m), 4.83 (2H, s), 4.86 (2H, s), 5.53 (1H, m), 7.1 (3H, m); ms: m/z 332 (M^+,13), 288 (3), 287 (5), 219 (7), 205 (28), 45 (100). Anal. Calcd for $C_{20}H_{28}O_4$: C, 76.26; H, 8.49. Found: C, 76.03; H, 8.38.

6-[2,5-Bis(methoxymethyloxy)benzyliden]-1,5,5-trimethylcyclohexene 17. This compound was prepared by the same procedure described above. Oil, 20% yield. Ir ($CHCl_3$) ν_{max} 2980, 2930, 1600, 1490, 1150, 1070 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.15 (6H, s), 1.25 (3H, s), 1.54 (4H, m), 3.45 (3H, s), 3.47 (3H, s), 5.06 (4H, s), 5.53 (1H, m), 6.35 (1H, s), 6.92 (3H, m); ms: m/z 332 (M^+,21), 317 (39), 287 (15), 45 (100). Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.01; H, 8.35.

3-[2-Hydroxy-5-methoxyphenyl]-4-[1,1-dimethyl-1-methoxymethyl]-1-methylcyclohexene 22. To a well stirred solution of **14** (450 mg, 1.41 mmol) in a 50:50 mixture THF-MeOH (20 ml) or only methanol (20 ml), 0.5 ml of conc hydrochloric acid was added and the mixture was stirred for 36 h at room temperature. After usual work-up the product was purified by column chromatography on silica gel using a 85:15 mixture of hexane-ethyl acetate as eluent affording **22** (135 mg, 33% yield) as oil. Ir ($CHCl_3$) ν_{max} 3200, 3009, 2940, 1610, 1590, 1490, 1150, 1050 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.21 (3H, s), 1.25 (3H, s), 1.73 (3H, s), 1.82 (3H, br), 2.15 (2H, m), 3.33 (3H, s), 3.73 (3H, s), 4.12 (1H, dd, J=7 Hz, J=6 Hz) 5.35 (1H, d, J=4 Hz), 6.72 (3H,m), 8.4 (1H, br, exchangeable with D_2O); ms: m/z 290 (M^+,22), 258 (49), 243 (25), 215 (39), 175 (100). Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found C, 74.37; H, 8.89.

1-[2,5-Bis(methoxymethyloxy)phenyl]-3-methyl-1,3-butadiene 18. A suspension of alcohol **10** (650 mg, 2.3 mmol) and Tonsil (Mexican bentonite) in 1:10 w/w ratio in 20 ml of acetone was heated under reflux for 18 h. After this time (the reaction was monitored by tlc), the tonsil was filtered and washed with acetone. The filtrate was concentrated and the residue was purified by column chromatography on silica gel using a mixture of hexane-ethyl acetate (9:1) to give **18** as colorless oil (420 mg, 69% yield). Ir ($CHCl_3$) ν_{max} 3005, 2980, 1600, 1580, 1490, 1150, 1070, 1010 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.97 (3H, s), 3.47 (3H, s), 3.49 (3H, s), 5.09 (2H, m), 5.13 (4H, s), 7.01 (5H, m); ms: m/z 264 (M^+,4), 249 (2), 219 (2), 45 (100). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.88; H, 7.48.

7-Hydroxy-1,3,4-trimethyl-1,2,3,4-tetrahydro-4a*H*-xanthene[21] 23. In a 50 ml round bottom flask 15 ml of a 50% solution of acetic acid, traces of conc H_2SO_4 and alcohol (**9**) (200 mg, 0.57 mmol) were placed and heated under reflux for 1 h. After the starting material had disappeared, (the reaction was monitored by

tlc) the reaction mixture was cooled, diluted with ethyl acetate and, a saturated solution of $NaHCO_3$ was added dropwise until neutralization. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3x10 ml). The combined organic layers were washed with water, dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel using a mixture of hexane-ethyl acetate 9:1 as eluent to give 50 mg (38%) of **23** as colorless oil. Ir ($CHCl_3$): ν_{max} 3604, 3018, 3967, 2933, 1612, 1584, 1493 cm^{-1}; 1239; ^{1}H-nmr ($CDCl_3$): δ 1.15 (3H, s), 1.23 (3H, s), 1.36 (3H, s), 1.65 (6H, m), 3.05 (1H, br, exchangeable with D_2O), 6.15 (1H, s), 6.55 (3H, m); ms: m/z 244 (M^+,39), 229 (100). Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.56; H, 8.17.

General procedure for the treatment of alcohols with tonsil in wet acetone.

2,2-Dimethyl-6-methoxychromene 25. In a 50 ml round bottom flask fitted with condenser and magnetic stirrer, 2.30 g (7.87 mmol) of alcohol **11**, 20 ml of acetone and 2 ml of distilled water were placed and heated under reflux for 12 h. The reaction was monitored by tlc. The tonsil was filtered and washed with acetone. The filtrate was dried over Na_2SO_4 and the solvent evaporated. The residue was chromatographed on silica gel and using a mixture of hexane-ethyl acetate 95:5 as eluent giving 958 mg (64%) of **25** as an oil. The spectral properties of this compound were found to be identical with those reported for the natural product.[14]

***O*-Methyldictyochromenol 29.** Prepared in 42% yield. Ir ($CHCl_3$) ν_{max} 3035, 2927, 1611, 1579, 1491, 1266, 1218, 1042 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.37 (3H, s) 1.62 (6H, br), 1.67 (3H, br), 2.04 (6H, m), 3.75 (3H, s), 5.05 (2H, m), 5.55, 6.25 (2H, d, AB, J=10 Hz), 6.58 (3H, m); ms: m/z 326 (M^+,7), 311 (1), 257 (1), 175 (100). Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26. Found: C, 80.81; H, 9.07.

***O*-Methylcordiachromene 27.** Prepared in 29% yield. Ir ($CHCl_3$) ν_{max} 3023, 2953, 1617, 1597, 1492, 1127, 1080 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.39 (3H, s), 1.57 (3H, s), 1.67 (3H, s), 2.09 (4H, m), 3.87 (3H, s), 5.12 (1H, m), 5.67, 6.02 (2H, ABq, J=10 Hz), 6.63 (3H, m); ms: m/z 258 (M^+,12), 243 (3), 189 (7), 175 (100). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.26; H, 8.62.

***cis*-6,6,9-Trimethyl-6a,7,8,10a-tetrahydro-6*H*-dibenzo[*b,d*]pyran-2-ol. 30 and its *O*-Methyl derivative 31.** To a well stirred solution of alcohols (**12-15**) (2.0 mmol) in 15 ml of THF was added 1 ml of 6N hydrochloric acid in a 15:1 v/v ratio or 15 ml of CH_2Cl_2, 50% solution of acetic acid with traces of H_2SO_4 (1 ml) and the mixture was heated to 45°C for 2 h. After this time, the solvent was removed under reduced pressure without heating. The residue was diluted with ether and washed with a saturated solution of

$NaHCO_3$, water, dried over anhydrous Na_2SO_4 and the solvent was evaporated. The residue was chromatographed on silica gel using a 9:1 mixture of hexane-ethyl acetate to afford benzopyran (**30**) in 84% and (**31**) in 60% yield respectively. Compound **30**; oil. Ir ($CHCl_3$) ν_{max} 3600, 3400, 1615, 1590, 1490, 1180, 1140 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.25 (3H, s), 1.40 (3H, s), 1.52 (2H, m), 1.68 (3H, s), 1.93 (2H, m), 1.96 (1H, m), 3.45 (1H, br), 4.52 (1H, br, exchangeable with D_2O), 5.82 (1H, br), 6.75 (3H, m); ms: m/z 244 (M^+,56), 229 (25), 201 (42), 161 (100). Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.50; H, 8.32. Compound **31**; oil. Ir ($CHCl_3$) ν_{max} 2975, 2932, 1612, 1595, 1491, 1265, 1140, 1041 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 1.25 (3H, s), 1.42 (3H, s), 1.50 (2H, m), 1.71 (3H, s), 1.93 (2H, m), 1.95 (1H, m), 3.35 (1H, br), 3.75 (3H, s), 5.85 (1H, br), 6.72 (3H, m); ms: m/z 258 (M^+,45), 243 (18), 215 (29), 175 (100). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.25; H, 8.43.

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Received, 20th August, 1993