Synthesis of 7-Acetyloxy-3,7-dimethyl-7,8-dihydro-6*H*-isochromene-6,8-dione and its Analogues

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7-Alkanoyloxy-3,7-dimethyl-7,8-dihydro-6*H*-isochromene-6,8-diones **12-15** were synthesized in 69-16% yields from the reaction of 2,4-dihydroxy-3-methyl-6-(2-oxopropyl)benzaldehyde **11** with *p*-toluenesulfonic acid in various carboxylic acids such as acetic acid, propionic acid, butyric acid and heptanoic acid followed by oxidation with lead tetraacetate. On the other hand, (±)-daldinin A **5** (oleate) was not obtained using oleic acid as a medium. In the cases of heptanoic acid and oleic acid, esters **16** and **17** were produced in 23 and 9% yields, respectively. 6,8-Dihydroxy-3,7-dimethyl-2-benzopyrylium *p*-toluenesulfonate **31** is considered as the intermediate for the production of **12-15**. Overall yields of isochromenes **12-15** were 26-6% starting from 2-methylresorcinol for seven steps.

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Introduction

Monascorubrin **1** [1], rubropunctatin **2** [2], (+)-sclerotiorin **3** [3], (-)-mitorubrin **4** [4] and daldinin A **5** (a mixture of four fatty acid esters) [5] are fungal metabolites produced by fungus such as *Monascus purpureus* Wentii, *M. rubropunctatus* Sâto, *Penicillium sclerotiorum* van Beyma, *P. rubrum* and *Daldinia concentrica*, respectively. Those compounds are called azaphilones because of the affinity for ammonia or amine, yielding vinylogous γ-pyridones [6]. Biosynthesis [7], total synthesis [8], toxicity [9] and biological activities [10] of azaphilones and their analogues have been investigated from the viewpoint of chemical, biological and pharmaceutical interests. Whalley and co-workers reported the synthesis of sclerotiorin **3** and tetrahydrosclerotiorin **6** as shown in Scheme 1. Compound **3** was obtained from formyl ketone **7** by treatment with phosphorus pentoxide in ethanol followed by lead tetraacetate oxidation of pyronoquinone **8** in acetic acid in 7% yield for two steps [8c,8d]. Similarily, compound **6** was prepared by the reaction of tetrahydro formyl ketone **9** with hydrogen chloride in ether and oxidation of the resulting pyrylium salt **10** with lead tetraacetate in acetic acid in 15% yield for two steps [11]. Thus, pyronoquinones and pyrylium salts are the important intermediates for the synthesis of azaphilones. In this paper we report a convenient synthesis of 2,4-dihydroxy-3-methyl-6-(2-oxopropyl)benzaldehyde **11** and efficient synthesis of 7-alkanoyloxy-3,7-dimethyl-7,8-dihydro-6*H*-isochromene-6,8-diones **12-15** by the reaction of **11** with *p*-toluenesulfonic acid (*p*-TsOH) followed by lead tetraacetate oxidation in various carboxylic acids. The mechanisms for the formation of **12-15** and esters **16** and **17**are discussed.

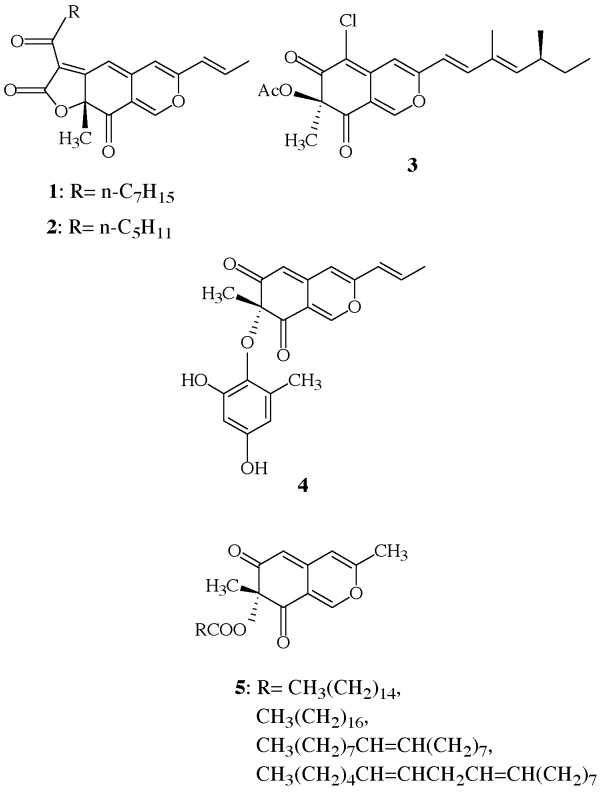
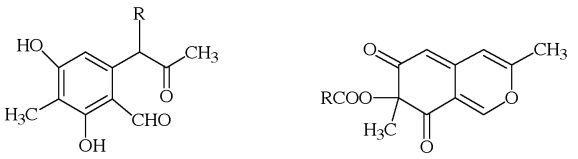


Figure 1

Results and Discussion

We attempted convenient synthesis of ketone **18**, which is a precursor of formyl ketone **11** in two ways. The first synthetic pathway is shown in Scheme 2. The hydroxyl group of 2-methylresorcinol was protected by treatment with dimethyl sulfate in 1.7 *M* aqueous sodium hydroxide solution under nitrogen to give 2-hydroxy-6-methoxytoluene **19** (66%) and 2,6-dimethoxytoluene **20** (30%) [12]. Compound **20** was identified by comparison with an authentic sample obtained by the reported procedure [13] and quantitatively converted to the corresponding monomethyl ether **19** by refluxing with sodium



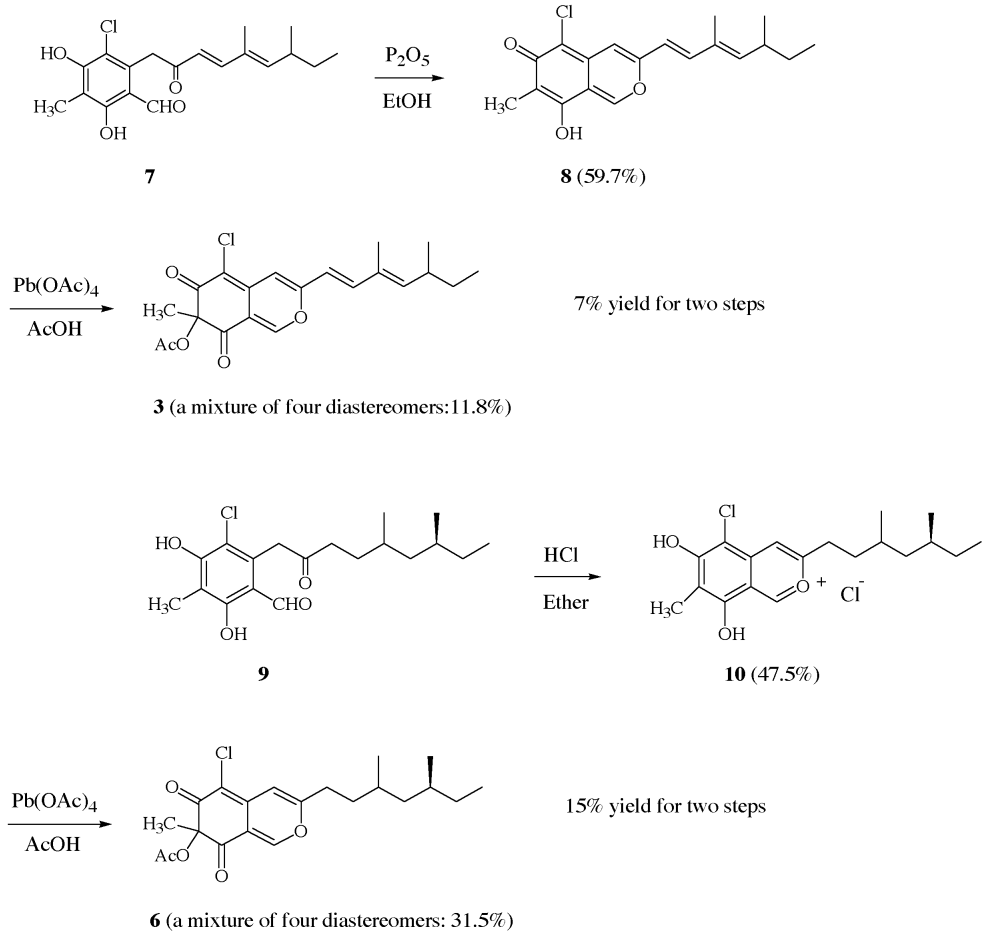
11: R=H
16: R=$CH_3(CH_2)_5COO$
17: R=$CH_3(CH_2)_7CH{=}CH(CH_2)_7COO$
12: R=CH_3
13: R=CH_3CH_2
14: R=$CH_3CH_2CH_2$
15: R=$CH_3(CH_2)_5$

Figure 2

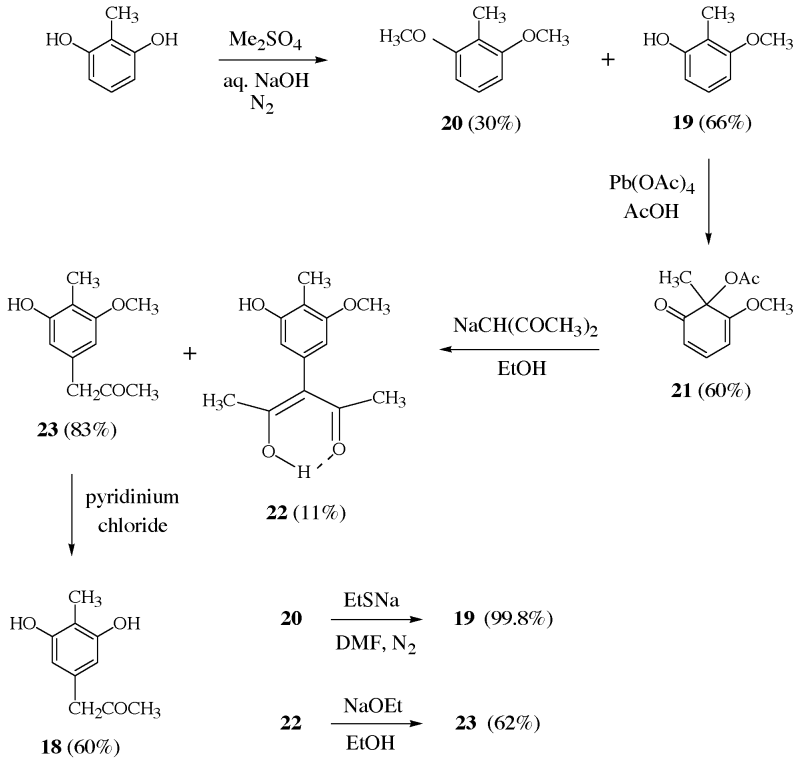
ethyl sulfide in dry *N*,*N*-dimethylformamide (DMF) [14]. Compound **19** was oxidized with lead tetraacetate in acetic acid to give 6-acetyloxy-5-methoxy-6-methylcyclohexa-2,4-dienone **21** in 60% yield [12]. According to the modified method of Kishi *et al*. [15], dienone **21** was converted to a mixture of 2-hydroxy-3-(3-hydroxy-5-methoxy-4-methylphenyl)-2-pentene-4-one **22** and 1-(3-hydroxy-5-methoxy-4-methylphenyl)-2-propanone **23** by 1,4-addition of sodium acetylacetonate in 11 and 83 % yields, respectively. The former was also transformed into **23** by a retro-Claisen like reaction on **22** in the presence of NaOEt in 62% yield. Ketone **18** was obtained by heating of **23** with pyridinium chloride in 60% yield [15]. Thus, compound **18** was obtained from 2-methylresorcinol *via* six steps in 31% overall yield.

The second synthetic pathway of **18** is illustrated in Scheme 3. We adopted the benzyl group as protection of phenol to increase the yield of ketone **18** because of its ready cleavage by catalytic hydrogenation. 2,6-Dibenzyloxytoluene **24** [16] which was quantitatively obtained by treatment of 2-methylresorcinol with benzyl chloride and potassium phosphate in dimethyl sulfoxide (DMSO) was refluxed with 2.5 equivalents of sodium ethyl sulfide in dry DMF to give benzyl ether **25** [16] in 99% yield [14]. By oxidation of **25** with lead tetraacetate, dienone **26** (61%) was obtained together with 2-benzyloxy-3-methylbenzoquinone (**27**) (12%), 4,4-diacetyloxy-3-benzyloxy-2-methylcyclohexa-2,5-dienone (**28**) (4%)

Scheme 1



Scheme 2



and 6,6-diacetyloxy-3-benzyloxy-2-methylcyclohexa-2,4-dienone (**29**) (4%). The above oxidation of **25** gave dienone **26** in moderate yield since compounds **27-29** were formed by side reactions of **25** with lead tetraacetate in 20% total yield. Next, by the conjugated addition of sodium acetylacetonate to cyclohexadienone **26** in dry ethanol compound **30** was obtained in 90% yield. Debenzylation of **30** was performed smoothly by catalytic hydrogenation with 7% palladium-charcoal in ethanol to give compound **18** quantitatively. Thus, ketone **18** was synthesized starting from 2-methylresorcinol in 52.7% overall yield *via* five steps.

Formyl ketone **11** (72%), which was equivalent to pyrylium salt **31** and pyronoquinone **32** was obtained by formylation of **18** with ethyl orthoformate using aluminum

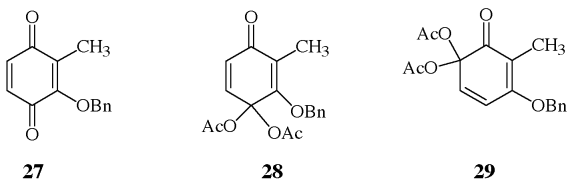
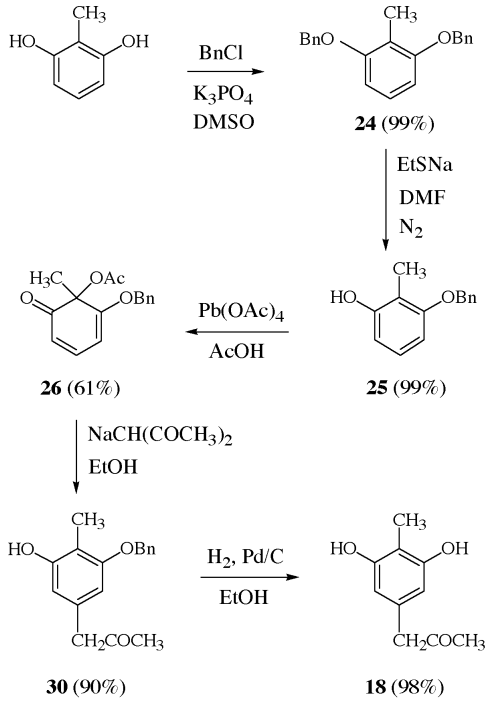


Figure 3

Scheme 3



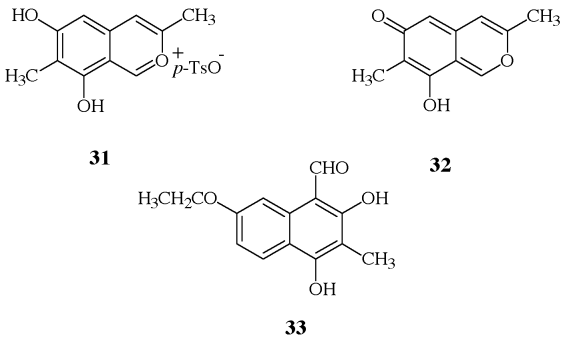


Figure 4

chloride as a catalyst in dry toluene [17] along with 7-ethoxy-2,4-dihydroxy-3-methyl-1-naphthaldehyde **33** (3%) [11].

Finally, isochromenes **12-15** and esters **16** and **17** were synthesized from the reaction of formyl ketone **11** with *p*-TsOH at 45-100° for 87-285 minutes and then with lead tetraacetate at 15-19° for 40-60 minutes in various carboxylic acids such as acetic acid, propionic acid, butyric acid, heptanoic acid and oleic acid, respectively. To complete the formation of pyrylium salt **31** without decomposition, reaction temperature in the range of 45-100° was employed. The results are listed in Table 1. When the reaction was carried out in acetic acid compound **12** was obtained in 69% yield (entry 1). In the cases of propionic acid and butyric acid, (entries 2 and 3), compounds **13** and **14** were produced in 38 and 26% yields, respectively. When heptanoic acid was employed as a medium, isochromene **15** and heptanoate **16** were obtained in 16 and 23% yields, respectively (entry 4). Furthermore, when the reaction was run in oleic acid oleate **17** was obtained in 9% yield and (±)-daldinin A **5** (oleate) was not produced (entry 5). In oleic acid the equilibrium between **11** and **31** might lie toward compound **11** as shown in Scheme 4 and compound **17** was obtained exclusively. By increasing the number of carbon atoms in the carboxylic acids, the yield of isochromene-6,8-diones was decreased and esters **16** and **17** were obtained in low yields.

Scheme 4

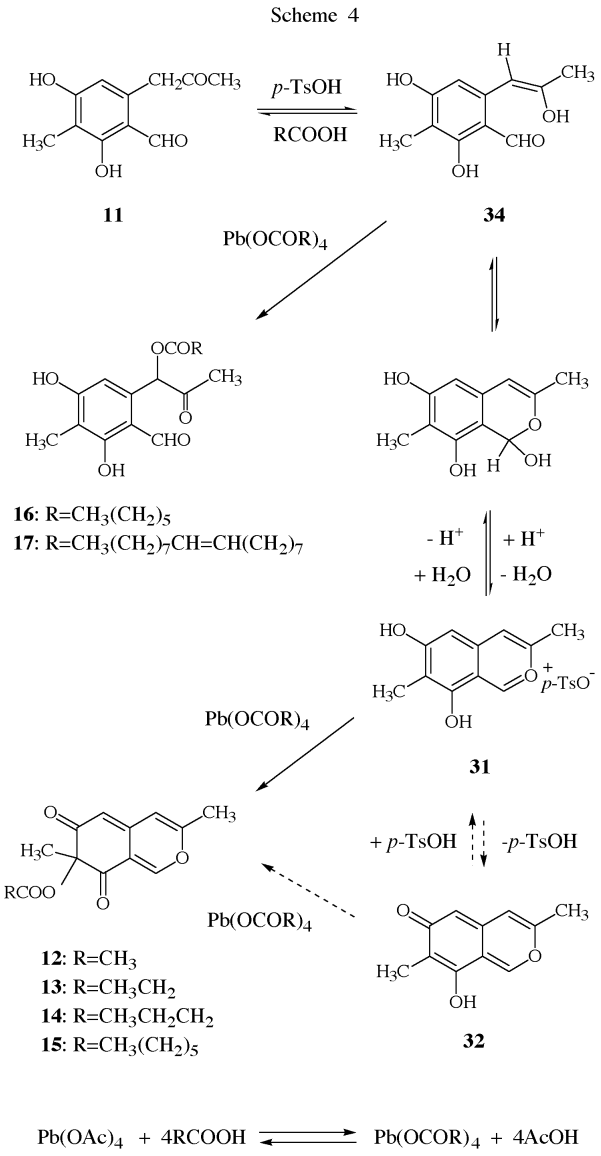


Table 1

Synthesis of Isochromenes **12-15** by the Reaction of **11** with *p*-TsOH Followed by Lead Tetraacetate in Various Carboxylic Acids

Entry	Solvent	*p*-TsOH/equiv.	Temp/°	Time/minutes	$Pb(OAc)_4$/equiv.	Temp/°	Time/min	Product (Yield/%)
1 [a]	Acetic Acid	20	100	90	1.34	15-17	45	**12** (69)
2 [b]	Propionic Acid	20	60	150	1.43	15-17	60	**13** (38)
3 [c]	Butyric Acid	20	90-95	87	1.35	15-17	40	**14** (26)
4 [d]	Heptanoic Acid	15	50	240	1.44	17-19	60	**15** (16), **16** (23)
5 [e]	Oleic Acid	15	45	285	1.45	18-19	60	**17** (9)

[a] **11**: 0.576 mmoles; Solvent: 115 ml. The oxidation stage was carried out under nitrogen. [b] **11**: 0.288 mmoles; Solvent: 58 ml. The oxidation stage was carried out under an argon atmosphere. [c] **11**: 0.288 mmoles: Solvent: 40 ml. The oxidation stage was carried out under an argon atmosphere. [d] **11**: 0.288 mmoles; Solvent: 58 ml. The oxidation stage was carried out under an argon atmosphere. [e] **11**: 0.288 mmoles; Solvent: 58 ml; Molecular Sives 4 Å: 1 g. The all reactions were carried out under an argon atmosphere.

A suitable mechanisms for the formation of isochromenes **12-15** and esters **16** and **17** are illustrated in Scheme 4. The ketone compound **11** exists in equilibrium with the corresponding enol form **34** which cyclizes to the pyrylium salt **31** *via* a hemiacetal in the presence of *p*-TsOH. The formation of pyrylium salt **31** was confirmed by ^{1}H and ^{13}C nmr measurements as described below (Table 2). Subsequently, by the oxidation of pyrylium salt **31** with lead tetraacetate or lead tetracarboxlates, which was produced by an exchange reaction between lead tetraacetate and the corresponding carboxylic acids [21], isochromenes **12-15** were produced undoubtedly [11]. These compounds were not formed *via* pyronoquinone **32** under these reaction conditions because compound **32** was not detected by ^{1}H and ^{13}C nmr measurements as described below. Esters **16** and **17** were produced by the oxidation of enol **34** with the corresponding lead tetracarboxylates, respectively [22].

of **31**, which was formed by the reaction of **11** with 1.5 equivalents of *p*-TsOH in CD_3COOD, confirmed the structure of **31**. In the ^{13}C spectrum, the peaks corresponding to the C1 and C3 carbon atoms were shifted to 164.8 and 175.6 ppm by effect of positive charge at the corresponding carbon atoms, respectively [19].

The structure of pyrylium salts was confirmed furthermore by using a 68% solution of perchloric acid-*d* in D_2O as an acid. In this case, compound **35** was formed completely by mixing of **11** with 5.4 equivalents of $DClO_4$ in CD_3OD for 1.4 hours at ambient temperature. The ^{1}H and ^{13}C nmr spectra of **35** were similar to that described for compound **31**. The ^{1}H nmr spectrum showed the two methyl hydrogen signals of C_7-CH_3 and C_3-CH_3 at δ 2.17 and 2.66, respectively and the three hydrogen signals of C_5-H, C_4-H and C_1-H at δ 6.74, 7.50 and 9.58, respectively. The peak of C_1-H was also located at lower magnetic field by positive charge at the C_1 carbon atom [18]. In the ^{13}C nmr spectrum,

Table 2

The ^{1}H and ^{13}C nmr Spectral Data and Deuterium Incorporation of Pyrylium Salts **31** and **35**

Compound	^{1}H nmr [a]/ppm	^{13}C nmr [b]/ppm	Deuterium incorporation [c] Site/%	
31	2.19 (s, 3H, C_7-CH_3)	8.9, 19.6, 103.8	C_4	76
	2.59 (s, 3H, C_3-CH_3)	114.4, 114.6, 116.2	C_5	42
	6.94 (s, 1H, C_5-H)	141.4, 160.4, 162.3		
	9.54 (s, 1H, C_1-H)	164.8, 175.6		
35	2.17 (s, 3H, C_7-CH_3)	8.6 (q), 19.4 (q)	C_4	39
	2.66 (s, 3H, C_3-CH_3)	103.2 (d), 114.5 (d)	C_5	93
	6.74 (s, 1H, C_5-H)	115.0 (s), 116.0 (s)		
	7.50 (s, 1H, C_4-H)	141.9 (s), 160.8 (s)		
	9.58 (s, 1H, C_1-H)	162.6 (s), 164.7 (d)		
		175.8 (s)		

[a] The ^{1}H nmr spectra of **31** and **35** were measures at 60 MHz, respectively. Preparation of **31**: **11**: 25.3 mg (0.122 mmoles); *p*-TsOH·H_2O: 109.3 mg (0.575 mmoles); CD_3COOD: 0.5 ml. Preparation of **35**: **11**: 25.3 mg (0.122 mmoles); a 68% solution of $DClO_4$ in D_2O (Aldrich): 98.5 mg (0.660 mmoles); CD_3OD: 0.4 ml. [b] The ^{13}C nmr spectrum of **31**, which was prepared by dissolving **11** and *p*-TsOH·H_2O in CD_3COOD (0.6 ml) in a 1:1.5 molar ratio and allowed to stand at room temperature for 13 hours, was measured at 125.7MHz. The ^{13}C nmr spectrum of **35** was measured at 22.49 MHz. Seventy percent aqueous $HClO_4$ was used instead of a 68% solution of $DClO_4$ in D_2O. [c] The deuterium incorporations at the C_4 and C_5 positions were calculated by the comparison of integral values of C_6-CH_2 and C_5-H to that of CHO in **11**, respectively.

Salt **31** was formed quantitatively in the nmr tube by treatment of compound **11** with 4.7 equivalents of *p*-TsOH in CD_3COOD for 3 hours at room temperature. The ^{1}H nmr spectra were measured at 60 MHz, and the results are listed at Table 2. In the ^{1}H nmr spectrum of **31**, singlets at δ 2.19 and 2.59 are assigned to the two methyl groups at the C_7 and C_3 positions, respectively and singlets at δ 6.94 and 9.54 to the two hydrogen atoms at the C_5 and C_1 positions, respectively. The peak corresponding to C_1-H was shifted to lower magnetic field by positive charge at the C_1 carbon atom [18]. The signal of C_4-H was not measured due to overlap with four peaks corresponding to the aromatic hydrogen atoms of *p*-TsOH. The ^{13}C nmr data the peaks of C_1 and C_3 carbon atoms were shifted to164.7 and 175.8 ppm by effect of positive charge at the corresponding carbon atoms, respectively [19]. There was no evidence for the formation of pyronoquinone **32** in the ^{1}H and ^{13}C nmr spectra (within limits of detection).

Additionally, chemical properties of **31** and **35** were revealed by deuterium-hydrogen exchange as shown in Table 2 [20]. Deuterium incorporation at the C_4 and C_5 positions in **31** were 76 and 42%, respectively and those in **35** were 39 and 93%, respectively. On the other hand, the hydrogen atom at the C_1 position of **31** and **35** was not deuterated. This result supports the fact that the positive charge is located at the C_1 carbon atom more than the C_4 and C_5 carbon atoms.

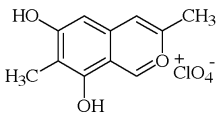


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Figure 5

In conclusion, 7-alkanoyloxy-3,7-dimethyl-7,8-dihydro-6*H*-isochromene-6,8-diones **12-15** were prepared by treatment of **11** with *p*-TsOH followed by lead tetraacetate in various carboxylic acids such as acetic acid, propionic acid, butyric acid, and heptanoic acid in 69-16% yields, respectively. By using oleic acid as a solvent, the corresponding isochromene, (±)-daldinin A **5** (oleate), was not produced. Esters **16** and **17** were formed as by-products in 23 and 9% yields by the reaction of enol **34** with the corresponding lead tetracarboxylates, respectively. Pyrylium salt **31**, which was detected by ^{1}H and ^{13}C nmr measurements, was the intermediate for the production of isochromenes **12-15**.

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were determined on a HITACH I-3000 spectrophotometer. The nuclear magnetic resonance spectra (^{1}H and ^{13}C) were measured on a JEOL JNM-FX 90Q FT NMR spectrometer (90MHz and 22.49 MHz, respectively) or a HITACHI R-24B NMR spectrometer (60 MHz), using tetramethylsilane as the internal standard. Unless otherwise stated silica gel (Wakogel C-200) was employed for the column chromatography as the packing material and anhydrous sodium sulfate as the drying agent. Ethanol was dried over molecular sieves 4 Å. DMF was dried over calcium hydride, distilled and stored over molecular sieves 4 Å under an argon atmosphere. Toluene was dried by refluxing with sodium, distilled and stored over molecular sieves 4 Å under an argon atmosphere. Ether refers to diethyl ether. The following compounds were prepared according to reported procedures: 2-hydroxy-6-methoxytoluene **19** [12], 6-acetyloxy-5-methoxy-6-methylcyclohexa-2,4-dienone **21** [12] and 2,6-dimethoxytoluene **20** [13].

General Procedure for the Reaction of Formyl Ketone **11** with *p*-Toluenesulfonic Acid Followed by Lead Tetraacetate in Various Carboxylic Acids.

A mixture of **11** (120 mg, 0.576 mmole), *p*-TsOH•H_2O (2.192 g, 11.52 mmoles) and acetic acid (115 ml) was heated at 100° for 1.5 hours under stirring. After cooling, a solid addition flask containing 95% lead tetraacetate (361 mg, 0.773 mmole) was attached to the reaction vessel *via* a nylon tube and the reaction flask was swept with a stream of nitrogen at 15° for 1 hour until all the air had been displaced. Lead tetraacetate was added in portions to the stirred solution at the same temperature over a period of 15 minutes and then allowed to stand at 15-17° for 40 minutes under nitrogen. The reaction mixture was poured into ice water (300 ml) and extracted two times with benzene (200 ml). The combined extracts were washed with brine, dried and concentrated under reduced pressure. The residue (123 mg) was chromatographed on silica gel (40 g). Compound **12** (99.2 mg, 69%) was obtained by elution with benzene-ether (5 :1).

For the elution of compounds **13-17**, the ratio of benzene to ether was varied from 1:0 to 5:2.

7-Acetyloxy-3,7-dimethyl-7,8-dihydro-6*H*-isochromene-6,8-dione (**12**)

Compound **12** was obtained as yellow plates, mp 178-179° (from benzene-ether); ir (potassium bromide): 3084, 2996, 2924, 1744 (COO), 1716, 1676, 1632 (C=C), 1590, 1552, 1446, 1327, 1336, 1250, 1228, 1136, 1120, 1086, 974, 938, 904, 882, 868, 472, 440, 420 cm^{-1} ; ^{1}H nmr (deuteriochloroform, 90 MHz): δ 1.57 (s, 3H, C_7-CH_3), 2.17 (s, 6H, C_3-CH_3 and $OCOCH_3$), 5.50 (d, 1H, J = 0.9 Hz, C_5-H), 6.10 (broad s, 1H, C_4-H), 7.86 (d, 1H, J = 0.9 Hz, C_1-H); ^{13}C nmr (deuteriochloroform): δ 19.2 (q), 20.1 (q), 22.3 (q), 84.4 (s), 106.7 (d), 109.2 (d), 115.2 (s), 142.6 (s), 153,7 (d), 158.6 (s), 169.9 (s), 192.6 (s), 193.2 (s).

Anal. Calcd. for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 62.88; H, 4.89.

3,7-Dimethyl-7-propionyloxy-7,8-dihydro-6*H*-isochromene-6,8-dione (**13**).

Compound **13** (38%) was obtained as yellow oil; ir (neat): 3076, 2988, 2944, 2928, 1740 (COO), 1720, 1674, 1644 (C=C), 1596, 1552, 1446, 1362, 1332, 1228, 1192, 1180, 1136, 1118, 1088, 968, 902, 868 cm^{-1}; ^{1}H nmr (deuteriochloroform, 60 MHz): δ 1.12 (t, 3H, J = 7.2 Hz, $OCOCH_2CH_3$), 1.50 (s, 3H, C_7-CH_3), 2.15 (s, 3H, C_3-CH_3), 2.46 (q, 2H, J = 7.2 Hz, $OCOCH_2CH_3$), 5.50 (s, 1H, C_5-H), 6.10 (s, 1H, C_4-H), 7.86 (s, 1H, C_1-H).

Anal. Calcd. for C_{14} $H_{14}O_5$: C, 64.12; H, 5.38. Found: C, 63.82; H, 5.52.

7-Butyryloxy-3,7-dimethyl-7,8-dihydro-6*H*-isochromene-6,8-dione (**14**).

Compound **14** (26%) was obtained as pale yellow oil; ir (neat): 3084, 2976, 2932, 2876, 1740 (COO), 1716, 1678, 1642 (C=C), 1592, 1550, 1448, 1334, 1224, 1134, 1116, 1080, 936, 902, 864 cm^{-1}; ^{1}H nmr (deuteriochloroform, 60 MHz): δ 0.97 (t, 3H, J = 6.6 Hz, $OCO(CH_2)_2CH_3$), 1.50 (s, 3H, C_7-CH_3), 1.67 (sextet, 2H, J = 6.6 Hz, $OCOCH_2CH_2CH_3$), 2.15 (s, 3H, C_3-CH_3), 2.41 (t, 2H, J = 6.6 Hz, $OCOCH_2CH_2CH_3$), 5.50 (s, 1H, C_5-H), 6.10 (s, 1H, C_4-H), 7.86 (s, 1H, C_1-H).

Anal. Calcd. for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 64.95; H, 5.90.

7-Heptanoyloxy-3,7-dimethyl-7,8-dihydro-6*H*-isochromene-6,8-dione (**15**).

Compound **15** (16%) was obtained as yellow oil; ir (neat): 3080, 2944, 2932, 2864, 1738 (COO), 1722, 1676, 1646 (C=C), 1600, 1554, 1454, 1446, 1332, 1230, 1170, 1136, 1120, 1090, 902, 868 cm^{-1}; ^{1}H nmr (deuteriochloroform, 60 MHz): δ 0.82-2.62 (m, 13H, $OCO(CH_2)_5CH_3$), 1.52 (s, 3H, C_7-CH_3), 2.16 (s, 3H, C_3-CH_3), 5.54 (s, 1H, C_5-H), 5.89 (s, 1H, C_4-H), 7.83 (s, 1H, C_1-H).

Anal. Calcd. for $C_{18}H_{22}O_5$: C, 67.91; H, 6.96. Found: C, 67.53; H, 6.86.

1-(2-Formyl-3,5-dihydroxy-4-methylphenyl)-1-heptanoyloxy-2-propanone (**16**).

Compound **16** (23%) was obtained as colorless oil; ir (neat): 2956, 2932, 2860, 1740 (COO), 1728, 1622, 1494, 1456, 1416, 1360, 1310, 1248, 1166, 1124, 1038 cm^{-1}; ^1H nmr (deuteriochloroform, 60 MHz): δ 0.89 (t, 3H, J = 6.6 Hz, $OCO(CH_2)_5CH_3$), 1.27 - 2.46 (m, 10H, $OCO(CH_2)_5CH_3$), 2.11 (s, 3H, $COCH_3$), 2.17 (s, 3H, C_4-CH_3), 6.29 (s, 1H, C_6-H or C_1-H), 6.50 (s, 1H, C_6-H or C_1-H), 10.10 (s, 1H, CHO), 12.78 (s, 1H, C_3-OH).

Anal. Calcd. for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.16; H, 7.28.

1-(2-Formyl-3,5-dihydroxy-4-methylphenyl)-1-oleoyloxy-2-propanone (**17**).

Compound **17** (9.4%) was obtained as colorless oil; ir (neat): 2928, 2856, 1718, 1624, 1464, 1414, 1308, 1248, 1174, 1124 cm^{-1}; ^1H nmr (deuteriochloroform, 60 MHz): δ 0.87 (t, 3H, J = 6.6 Hz, $(CH_2)_7CH_3$), 1.28 - 2.42 (m, 28H, two $(CH_2)_7$), 2.10 (s, 3H, $COCH_3$), 2.15 (s, 3H, C_4-CH_3), 5.33 (broad t, 2H, J = 6.6 Hz, CH=CH), 6.29 (s, 1H, C_6-H or C_1-H), 6.48 (s, 1H, C_6 - H or C_1-H), 10.09 (s, 1H, CHO), 12.86 (s, 1H, C_3-OH).

Anal. Calcd for $C_{29}H_{44}O_6$: C, 71.28; H, 9.08. Found: C, 71.51; H, 9.39.

2-Hydroxy-3-(3-hydroxy-5-methoxy-4-methylphenyl)-2-pentene-4-one (**22**) and 1-(3-Hydroxy-5-methoxy-4-methylphenyl)-2-propanone (**23**).

To a stirred solution of sodium metal (720 mg, 31.1 mmoles) in dry ethanol (220 ml) was added acetylacetone (15.3 g, 0.15 mole) dropwise and then the dienone **21** [12] (3.05 g, 15.3 mmoles) in dry ethanol (120 ml). The reaction mixture was refluxed for 15 hours at 90° (oil bath temperature). After cooling, aqueous 3 *M* hydrochloric acid (150 ml) was poured into the reaction mixture. The residue obtained upon evaporation of ethanol *in vacuo* was extracted with ether. The ethereal solution was washed with water, dried and evaporated to give the oily residue. Compounds **22** (0.39 g, 11%) and **23** (2.47 g, 83%) were obtained by chromatography on silica gel using benzene-acetonitrile (4:1) as eluent.

Compound **22** (enol form) was obtained as colorless short needles, mp 101-102° (from benzene-hexane); ir (potassium bromide): 3380 (OH), 3196, 3012, 2956, 2936, 2864, 2844, 1616, 1592, 1522, 1414, 1360, 1336, 1228, 1120, 848, 736, 660 cm^{-1}; ^1H nmr (deuteriochloroform, 60 MHz): δ 1.90 (s, 6H, two CH_3), 2.10 (s, 3H, C_4-CH_3), 3.77 (s, 3H, C_5-OCH_3), 5.27 (s, 1H, C_3-OH), 6.24 (s, 2H, C_2-H and C_6-H) and 16.41 (s, 1H, C_2-OH); ^{13}C nmr (deuteriochloroform, 50 MHz): δ 8.0, 24.0, 55.8, 105.6, 110.7, 111.6, 115.4, 134.9, 154.8, 158.8, 191.2; ms: m/z 236 (M^+), 221, 193, (M^+-$COCH_3$), 161, 43 ($COCH_3^+$).

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.09; H, 6.82. Found: C, 66.19; H, 6.90.

Compound **23** was obtained as colorless oil, bp 136° at 0.34 Torr; ir (neat): 3404 (OH), 3004, 2940, 2844, 1702 (CO), 1616, 1598, 1520, 1464, 1454, 1428, 1358, 1232, 1146, 1114, 844, 796 cm^{-1} ; ^1H nmr (deuteriochloroform, 60 MHz): δ 2.04 (s, 3H, CH_2COCH_3 or C_4-CH_3), 2.11 (s, 3H, C_4-CH_3 or CH_2COCH_3), 3.55 (s, 2H,CH_2COCH_3), 3.75 (s, 3H, OCH_3), 6.08 (s, 1H, OH) and 6.28 (s, 2H, C_2-H and C_6-H); ^{13}C nmr (deuteriochloroform): δ 7.9 (q), 28.9 (q), 51.0 (t), 55.8 (q), 104.1 (d), 109.1 (d), 111.3 (s), 132.4 (s), 154.9 (s), 158.8 (s) and 207.9 (s).

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.67; H, 7.35.

Conversion of **22** to **23**.

Compound **22** (118 mg, 0.499 mmole) was refluxed with sodium metal (24 mg, 1.04 mmoles) in dry ethanol (11.1 ml) for 2 hours. The reaction mixture work up was performed in a similar manner to that described for the synthesis of **22** and **23**. Phenylacetone **23** (60 mg, 62%) was prepared and identified by comparison with an authentic sample.

1-(3,5-Dihydroxy-4-methylphenyl)-2-propanone (**18**).

Method A.

A mixture of compound **23** (460 mg, 2.35 mmoles) and pyridinium chloride (2.72 g, 25.5 mmoles) was heated at 180° for 2 hours under mechanical stirring. After cooling, water was poured into the reaction mixture and the mixture was extracted with ether. The ethereal solution was washed with brine and dried. The residue obtained upon evaporation of ether was chromatographed on silica gel. Compound **18** (256 mg, 60%) was obtained by elution with benzene-ether (2:1) as colorless oil, which was identified by comparison of its nmr and ir spectral data with those of an authentic sample obtained by debenzylation of **30**.

Method B.

A mixture of **30** (150 mg, 0.55 mmole), 7% palladium on charcoal (34 mg) and ethanol (16 ml) was stirred under an atmospheric pressure of hydrogen at room temperature for 6 hours. The insoluble materials were removed by filtration and the filtrate was concentrated under reduced pressure. The residue was column chromatographed on silica gel (21 g). By elution with hexane-acetone (volume ratio was varied from 15:2 to 15:4) compound **18** was obtained as a colorless oil (97 mg, 98%), bp 205° at 1.4 Torr (bulb to bulb distillation); ir (neat): 3388 (OH), 2928, 1706, 1692, 1628, 1596, 1520, 1436, 1364, 1310, 1292, 1166, 1082, 842, 802, 768, 720, 676, 590 cm^{-1}; ^1H nmr (deuteriochloroform, 60 MHz): δ 2.09 (s, 3H, CH_2COCH_3 or C_4-CH_3), 2.14 (s, 3H, C_4-CH_3 or CH_2COCH_3), 3.52 (s, 2H, CH_2COCH_3), 5.72 (s, 2H, two OH), 6.23 (s, 2H, C_2-H and C_6-H); ^{13}C nmr (CD_3COCD_3): δ 8.4 (q), 28.9 (q), 50.6 (t), 108.8 (d), 110.3 (s), 133.2 (s), 156.6 (s), 208.8 (s).

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.53; H, 6.93.

2,6-Dibenzyloxytoluene (**24**).

A mixture of 2-methylresorcinol (**20**) (12.41 g, 0.10 mole), benzyl chloride (27.8 g, 0.22 mole), potassium phosphate (84.9 g, 0.4 mole) and 250 ml of DMSO was stirred at 60° for 80 minutes. After cooling, insoluble materials were removed by filtration. The residue obtained upon evaporation of DMSO under reduced pressure was poured into water and the mixture was extracted with ether (500 ml). The ethereal solution was washed with water, dried over anhydrous magnesium sulfate and evaporated *in vacuo*. Compound **24** [16] (30.1 g, 99%) was obtained as colorless columnar crystals, mp 80.0-80.7° (from methanol); ir (potassium bromide): 3032, 2912, 2860, 1594, 1500, 1476, 1456, 1378, 1272, 1250, 1104, 760, 754, 728, 696 cm^{-1}; ^1H nmr (deuteriochloroform, 60 MHz): δ 2.20 (s, 3H, CH_3), 5.02 (s, 4H, two $OCH_2C_6H_5$), 6.54 (d, 2H, J = 8.4 Hz, C_3-H and C_5-H), 7.04 (dd, J = 8.4 Hz, C_4-H), 7.33 (s, 10H, two $OCH_2C_6H_5$).

Anal. Calcd. for $C_{21}H_{20}O_2$: C, 82.87; H, 6.62. Found: C, 82.63; H, 6.65.

2-Benzyloxy-6-hydroxytoluene (**25**).

To a stirred suspention of 60% sodium hydride (1.68 g, 40 mmoles) in DMF (20 ml) was added dropwise 40 ml of a 1.0 *M* solution of ethanethiol in DMF by a syringe under nitrogen and then continued stirring for an additional 10 minutes. Dibenzyl ether **24** (4.88 g, 16 mmoles) in DMF (24 ml) was added dropwise to the stirred solution by a syringe under nitrogen and refluxed for 3 hours. After cooling, the reaction mixture was acidified with aqueous 1 *M* hydrochloric acid (900 ml) and extracted with ether (800 ml). The ethereal solution was washed with water, dried and evaporated *in vacuo* to give an oily residue (6.50 g). The residue was chromatographed on silica gel (Merck Kieselgel 60, 160 g). By elution with hexane-acetone (15:1) sulfur containing compounds were obtained. Next, by elution with hexane-acetone (10:1) compound **25** [16] (3.4 g, 99%) was obtained as colorless crystals, mp 58.0-58.5° (from benzene-hexane); ir (potassium bromide): 3308 (OH), 3028, 2924, 2884, 2848, 1612, 1598, 1506, 1472, 1448, 1380, 1274, 1238, 1168, 1112, 766, 732, 692 cm^{-1}; ^1H nmr (deuteriochloroform, 60 MHz): δ 2.16 (s, 3H, CH_3), 4.78 (s, 1H, OH), 5.02 (s, 2H, $OCH_2C_6H_5$), 6.41 (dd, 1H, J = 7.8 and 1.2 Hz, C_3-H or C_5-H), 6.49 (dd, 1H, J = 7.8 and 1.2 Hz, C_3-H or C_5-H), 6.98 (dd, 1H, J = 7.8 Hz, C_4-H), 7.35 (s, 5H, $OCH_2C_6H_5$).

Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.33; H, 6.57.

The Reaction of the Monobenzyl Ether **25** with Lead Tetraacetate.

To a stirred solution of 95% lead tetraacetate (7.0 g, 15.0 mmoles) in acetic acid (40 ml) was added compound **25** (1.45 g, 6.77 mmoles) in small portions at 15-17° over a period of 8 minutes and then 95% lead tetraacetate (7.2 g, 15.4 mmoles) added to the reaction mixture in small portions. Another monobenzyl ether **25** (2.90 g, 13.5 mmoles) was added portionwise to the above reaction mixture under stirring at the same temperature over a period of 8 minutes and the reaction mixture was allowed to stand at 15° for 30 minutes. The reaction mixture was poured into water (300 ml) and extracted two times with ether (600 ml). The combined ethereal solution was washed with water, dried and evaporated *in vacuo*. The remaining acetic acid in the residue was removed by azetoropic distillation with toluene under reduced pressure. The residue (5.91 g) was chromatographed on silica gel (320 g) contained 32 ml of distilled water. Firstly, **27** (0.583 g, 12.4%) was obtained by elution with hexane-acetone (30:1). Secondly, **28** (0.296 g, 4.4%), **25** (0.269 g, 6.2%) and **26** (3.39 g, 61.3%) were obtained by elution with hexane-acetone (15:1), respectively. Finally, **29** (0.289 g, 4.3%) was obtained by elution with hexane-acetone (2:1).

6-Acetyloxy-5-benzyloxy-6-methylcyclohexa-2,4-dienone (**26**).

Compound **26** was obtained as yellow prisms, mp 103.5-104.0° (from ethyl ether); ir (potassium bromide): 3072, 2988, 2952, 2936, 2892, 1748 (CO), 1674, 1628 (C=C), 1538, 1362, 1284, 1242, 1150, 1100, 1086, 1042, 968, 918, 878, 848, 816, 752, 726, 718, 696, 494 cm^{-1} ; uv (ethanol): λ_{max} (ε) 334 (5400) and 365 nm (4840, shoulder); ^1H nmr (deuteriochloroform, 60 MHz): δ 1.53 (s, 3H, C_6-CH_3), 2.06 (s, 3H, C_6-$OCOCH_3$), 4.90 (s, 2H, C_5-$OCH_2C_6H_5$), 5.40 (d, 1H, J = 7.2 Hz, C_4-H), 5.92 (d, 1H, J = 9.6 Hz, C_2-H), 7.08 (dd, 1H, J = 9.6 and 7.2 Hz, C_3-H), 7.32 (s, 5H, $OCH_2C_6H_5$).

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92. Found: C, 70.36; H, 5.91.

2-Benzyloxy-3-methylbenzoquinone (**27**).

Compound **27** was obtained as orange prisms, mp 49.0-50.0° (from hexane-ether); ir (potassium bromide): 3056, 2948, 2888, 1668 (CO), 1646 (C=C), 1598, 1500, 1454, 1374, 1308, 1218, 1176, 1086, 1022, 958, 848, 738, 694, 664 cm^{-1}; uv (ethanol): λ_{max} (ε) 366 (1200) and 252 nm (12200); ^1H nmr (deuteriochloroform, 60 MHz): δ 1.87 (s, 3H, C_3-CH_3), 5.29 (s, 2H, $OCH_2C_6H_5$), 6.61 (s, 2H, C_5-H and C_6-H), 7.34 (s, 5H, $OCH_2C_6H_5$).

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.50; H, 5.25.

4,4-Diacetyloxy-3-benzyloxy-2-methylcyclohexa-2,5-dienone (**28**).

Compound **28** was obtained as colorless short needles, mp 90.8-91.5° (from hexane-ether); ir (potassium bromide): 1768 and 1746 (COO), 1670 (CO), 1640, 1618 (C=C), 1456, 1372, 1320, 1296, 1244, 1282, 1130, 1094, 1002, 832, 754, 700 cm^{-1}; ^1H nmr (deuteriochloroform, 60 MHz): δ 1.94 (s, 3H, C_2-CH_3), 1.99 (s, 6H, two $OCOCH_3$), 5.18 (s, 2H, $OCH_2C_6H_5$), 6.27 (d, 1H, J = 11.4 Hz, C_6-H), 7.29 (d, 1H, J = 11.4 Hz, C_5-H) and 7.37 (s, 5H, $OCH_2C_6H_5$).

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.30; H, 5.49.

6,6-Diacetyloxy-3-benzyloxy-2-methylcyclohexa-2,4-dienone (**29**).

Compound **29** was obtained as yellow short needles, mp 138-141° (from acetone-hexane); ir (potassium bromide): 1754, (COO), 1664 (CO), 1652 (C=C), 1586, 1410, 1248, 1222, 1012, 952, 762 cm^{-1}; ^1H nmr (deuteriochloroform, 60 MHz): δ 1.86 (s, 3H, C_2-CH_3), 2.07 (s, 6H, two $OCOCH_3$), 5.14 (s, 2H, $OCH_2C_6H_5$), 6.60 (s, 2H, C_4-H and C_5-H), 7.35 (s, 5H, $OCH_2C_6H_5$).

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.48; H, 5.48.

1-(3-Benzyloxy-5-hydroxy-4-methylphenyl)-2-propanone (**30**).

To an ethanolic solution (280 ml) of sodium metal (217 mg, 9.43 mmoles) was added acetylacetone (4.631 g, 46.4 mmoles) followed by a solution of cyclohexadienone **26** (1.262 g, 4.64 mmoles) in dry ethanol (80 ml). The reaction mixture was refluxed for 17 hours, then acetylacetone (0.486 g, 4.85 mmoles) was added and refluxing was continued for additional 4 hours. After cooling, aqueous 6 *M* hydrochloric acid (8 ml) diluted with water (200 ml) was added into the reaction mixture and solvents were removed under reduced pressure. The residue was extracted with ether (500 ml), washed with brine and dried. The residue obtained upon evaporation of ether *in vacuo* was chromatographed on silica gel (Merck Kieselgel 60, 85 g). Compound **30** (1.128 g, 90%) was obtained by elution with hexane-acetone (10:1), hexane-benzene (30:4) and hexane-acetone (5:1). Ketone **30** was recrystallized from benzene-hexane to give colorless short needles, mp 77.9-78.4°; ir (potassium bromide): 3364 (OH), 3036, 2928, 2892, 2860, 1714 (CO), 1624, 1598, 1518, 1430, 1116, 858, 732, 692, 640, 548, 468 cm^{-1}; ^1H nmr (deuteriochloroform, 60 MHz): δ 2.08 (s, 3H, CH_2COCH_3 or

C_4-CH_3), 2.11 (s, 3H, C_4-CH_3 or CH_2COCH_3), 3.54 (s, 2H, CH_2COCH_3), 5.00 (s, 2H, $OCH_2C_6H_5$), 5.71 (s, 1H, OH), 6.32 (s, 2H, C_2-H and C_6-H), 7.34 (s, 5H, $OCH_2C_6H_5$).

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.44; H, 6.71.

2,4-Dihydroxy-3-methyl-6-(2-oxopropyl)benzaldehyde (**11**) and 7-Ethoxy-2,4-dihydroxy-3-methyl-1-naphthaldehyde (**33**).

To a suspension of 95% anhydrous aluminum chloride (314 mg, 2.24 mmoles) in dry toluene (2.58 ml) was added a solution of **18** (225 mg, 1.25 mmoles) and ethyl orthoformate (2.73 g, 17.5 mmoles) in dry toluene (2.58 ml) dropwise at -50° for 1 hour with stirring and then allowed to warm to -30° for over a period of 22 minutes and stirred at the same temperature for another 20 minutes. Aqueous 3 *M* hydrochloric acid (6 ml) was added and the mixture was stirred for 20 minutes. Water (7.2 ml) was poured into the reaction mixture and extracted with ether. The ethereal solution was washed with brine and dried. The residue obtained upon evaporation of ether *in vacuo* was chromatographed on silica gel (20 g). Aldehyde **33** (9.8 mg, 3%) and formyl ketone **11** (188 mg, 72%) were obtained by elution with hexane-acetone (10:1), respectively. Compound **18** (16 mg, 7%) was recovered subsequently by the elution with hexane-acetone (20:7).

Compound **11** was obtained as colorless prisms, mp 137.0-138.0° dec (from acetone-hexane); ir (potassium bromide): 3212 (OH), 2928, 2900, 1706 (CO), 1642, 1622 (CHO), 1426, 1324, 1314, 1302, 1254, 1170, 1124, 818, 802, 576, 560 cm^{-1}; ^1H nmr (acetone-d_6, 60 MHz): δ 2.04 (s, 3H, CH_2COCH_3 or C_3-CH_3), 2.21 (s, 3H, C_3-CH_3 or CH_2COCH_3), 4.09 (s, 2H, CH_2COCH_3), 6.38 (s, 1H, C_5-H), 9.30 (broad s, 1H, C_4-OH), 9.85 (s, 1H, CHO), 12.68 (broad s, 1H, C_2-OH); ^{13}C nmr (CD_3COCD_3): δ 7.3 (q), 29.5 (q), 46.7 (t), 110.8 (s), 111.6 (d), 113.3 (s), 138.9 (s), 163.5 (s), 164.7 (s), 194.4 (d), 205.6 (s).

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.52; H, 5.81.

Compound **33** was obtained as brown yellow short needles, mp 194.0-197.5° dec (from acetone-hexane); ir (potassium bromide): 3436, (OH), 3208 (OH), 2988, 2932, 1628 (CHO), 1598, 1416, 1328, 1246, 1222, 1158, 1050, 964, 802 cm^{-1}; ^1H nmr (CD_3COCD_3, 90 MHz): δ 1.43 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 2.23 (s, 3H, C_3-CH_3), 4.23 (2H, q, J = 7.1 Hz, OCH_2CH_3), 7.01 (dd, 1H, J = 9.2 and 2.6 Hz, C_6-H), 7.79 (1H, d, J = 2.6, C_8-H), 8.14 (d, 1H, J = 9.2 Hz, C_5-H), 9.06 (broad s, 1H, C_4-OH), 10.57 (s, 1H, CHO), 14.44 (s, 1H, C_2-OH); ^{13}C nmr (CD_3COCD_3): δ 7.8,(q), 15.1 (q), 64.5 (t), 101.3 (d), 107.1 (s), 107.2 (s), 115.7 (d), 116.1 (s), 125.5 (d), 136.1 (s), 160.3 (s), 160.7 (s), 168.6 (s), 192.0 (d).

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.09; H, 5.71.

The ^1H and ^{13}C nmr Measurements and Deuterium Exchange of Pyrylium Salt **31**.

Formyl ketone **11** (25.3 mg, 0.122 mmole) was dissolved in CD_3COOD (0.5 ml) in an nmr tube and then *p*-TsOH•H_2O (109.3 mg, 0.575 mmole) was added to the above solution. The color of the solution turned yellow immediately and deepened gradually in ambient temperature. After 3 hours the proton signals of compound **11** disappeared completely and only the proton signals of pyrylium salt **31** were remaining in ^1H nmr spectrum (60 MHz). The ^1H nmr spectral data of **31** are given at Table 2. After being maintained for 24 hours at room temperature from the time of mixing, the mixture was poured into a solution of potassium carbonate (1.442 g) in deuterium oxide (8 ml) and neutralized with aqueous 6 *M* hydrochloric acid. This aqueous solution work up was in the usual way to give deuterated compound **11** as crystals. Compound **11** was dissolved in CD_3COCD_3 and the ^1H nmr spectrum of **11** was measured at 60 MHz. The deuterium incorporation was calculated by comparison of the integral values of C_6-CH_2 and C_5-H with that of CHO. The results are listed in Table 2. A solution of **11** (38.8 mg, 0.234 mmole) and *p*-TsOH•H_2O (66.8 mg, 0.351 mmole) in CD_3COOD (0.6 ml) was allowed to stand at room temperature for 13 hours and the ^{13}C nmr spectrum of **31** was measured at 125.7 MHz. The results are summarized at Table 2.

The ^1H and ^{13}C NMR Measurements and Deuterium Exchange of Pyrylium Salt **35**.

Compound **11** (25.3 mg, 0.122 mmole) was dissolved in CD_3OD (0.4 ml) in an nmr tube and then 98.5 mg of 68% perchloric acid-*d* solution in deuterium oxide (67 mg, 0.660 mmole) was added to the solution. The color of the solution turned yellow and deepened quickly. After 1.4 hours the proton signals corresponding to **11** had disappeared and only the proton signals corresponding to **35** remained in ^1H nmr spectrum (60 MHz). The ^1H nmr spectral data of **35** are listed in Table 2. After maintaining the solution for 24 hours at ambient temperature with mixing, the methanol solution of **35** was poured into a solution of sodium acetate (82.2 mg) in CD_3OD (3 ml) and extracted with ether. The ethereal solution work up was in the usual way and gave the deuteriated compound **11** as crystals. Compound **11** was dissolved in CD_3COCD_3 and the ^1H nmr spectrum of **11** was measured at 60 MHz. Hydrogen-deuterium exchange of **11** was calculated in a similar manner as that described for **31**, and the results are listed in Table 2. The ^{13}C nmr spectrum of **35** in CD_3OD was measured by using aqueous 70% perchloric acid instead of a 68% solution of perchloric acid-*d* in D_2O; the results are shown in Table 2.

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