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DIHYDROISOCOUMARINS AND PHTHALIDE FROM WOOD SAMPLES INFESTED BY FUNGI*

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Abstract—Wood samples, infested by fungi during storage, were shown to contain, besides the known 5-methylmellein, additional (3*R*)-8-hydroxy-3-methyl-3,4-dihydroisocoumarins substituted by 7-methyl, 5-formyl, 5-carboxy, 5-hydroxy, 5-methoxy, 6-methoxy-5-methyl and 6,7-dimethoxy-5-methyl groups, as well as 6-formyl-7-hydroxy-5-methoxy-4-methylphthalide. Several 2-methylchromanones were synthesized in order to show that this class of compounds can be distinguished from 3-methyl-3,4-dihydroisocoumarins by MS.

INTRODUCTION

The compounds **1a–1f**, **2a**, **2b** and **3a** were isolated from 12 species belonging to 7 families of trees (Table 1). Several 3-methyl-3,4-dihydroisocoumarins and phthalides [1], as well as 5-hydroxy-2-methylchromanone [2] are typical metabolites of fungi, and, indeed, microscopic examination of wood samples 3, 11 and 12, performed by Dr. Ozorio J. M. Fonseca, revealed the presence of *Aspergillus*, *Penicillium*, *Fusarium* and *Trichoderma* species. Since in freshly cut samples of the same species neither polyketides, nor fungi could be detected, fungal invasion must have taken place during the drying and storage period between collection and extraction. The sites of storage, thousands of kilometers apart for samples belonging to different species (Table 1), did not affect the nature of the compounds, which all belong to the same biogenetic group. The introduction of an oxygen function at C-5 presumably through gradual oxidative transformation of Me (cf. **1a**) via CHO (**1c**), CO_2H (**1d**) to OH (**1e**) and OMe (**1f**), though unexceptional, is interesting.

Small amounts of shikimate–acetate derived compounds were found to co-occur in the extracts of *Rheedia gardneriana* [3]: 1,5-dihydroxyxanthone, 1,7-dihydroxyxanthone, 1,6-dihydroxy-5-methoxyxanthone; *Virola caducifolia* [4]: formononetin, biochanin A, virolane, virolanol; and *Virola venosa* [5]: 3-hydroxy-5-methoxystilbene and virolanol. While the remaining 9 extracts were found to be void of detectable quantities of shikimate–acetate derived phenolics, fatty acids (**4**) and esters (**5**) as well as sitosterol and stigmasterol (**6**) and sitostenone (**7**) were isolated in considerable quantities from all 12 samples (Table 1). Since several hundred wood samples, examined by us over the same period, were kept in the same storage facilities, lack of antibiotic phenolics, accumulation of fatty or steroidal material or both seem to justify fungal invasion.

RESULTS

Expansions of the molecular formulae, based on PMR spectra, reveal the compounds to be trisubstituted (**1a–1f**), tetrasubstituted (**2a**) and pentasubstituted (**2b**, **3a**) benzoyl derivatives. The spectra show additionally that the aromatic protons in all trisubstituted derivatives are vicinal and that the hydroxyls in all derivatives are chelated (τ *ca* −1). This fact is confirmed by UV $AlCl_3$-shifts. The OCH . Me . CH_2 units of **1a–1f**, **2a**, **2b** and the OCH_2 unit of **3a** could, *a priori*, be part of two pairs of fundamental skeleta, respectively **8** or **9** and **10** or **11**. While the phthalide skeleton (**10**) can be adopted for **3a** (ν_{max} 1742 cm^{-1}) in preference to the coumaranone alternative (**11**) which should give rise to a carbonyl band at considerably lower frequency [6], discrimination of chelated dihydroisocoumarins (**8**) and chromanones (**9**) is difficult (for both ν_{max} 1660–1670 cm^{-1}). It was necessary to measure the carbonyl frequency of the methyl ethers **1g** and **1h** (ν_{max} *ca* 1725 cm^{-1}) in order to obtain evidence that these compound are esters (**8**) and not ketones (**9**). It was considered that a more reliable distinction between structural types **8** and **9** may be possible by PMR. Clearly, splitting of the $OCHCH_2$ proton bands will be highly sensitive to conformation of

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Table 1. Sources of compounds

Species	Sites of collection/ extraction	Compounds (mg/kg of trunk wood)
1 *Anacardium parvifolium* Engl. Anacardiaceae	Manaus/ Manaus	**1a** (6), **1c** (5), **4** (740), **6** (260)
2 *Rheedia gardneriana* Pl. *et* Tr. Guttiferae	Recife/ Belo Horizonte	**1a**, **5** (23), **6** (123)
3 *Endlicheria sericea* Nees Lauraceae	Manaus/ Manaus	**1a** (39), **1b** (11), **1f** (9) **2a** (10), **6** (220), **7** (6)
4 *Ocotea argyrophylla* Ducke Lauraceae	Manaus/ Manaus	**1a** (260), **1f** (38), **5**, **6** (338)
5 *Hymenaea oblongifolia* Hub. Leguminosae-Caesalpinioideae	Belém/ Rio de Janeiro	**3a** (4), **4** (30), **5** (156), **6** (29)
6 *Macrolobium bifolium* (Aubl.) Pers. Leguminosae-Caesalpinioideae	Belém/ Rio de Janeiro	**1a** (7), **1f** (14), **3a** (11), **4** (9), **6** (94), **7** (5)
7 *Mora paraensis* Ducke Leguminosae-Caesalpinioideae	Belém/ Rio de Janeiro	**1a** (10)
8 *Virola caducifolia* W. Rodr. Myristicaceae	Manaus/ Manaus	**1d** (5), **4**, **5**, **6**
9 *Virola venosa* (Benth) Warb Myristicaceae	Manaus/ Manaus	**1d** (13), **1e** (20), **1f** (4), **4** (25), **6** (33)
10 *Panopsis sessilifolia* (Rich.) Sandw. Proteaceae	Belém/ Rio de Janeiro	**1a** (82), **2a** (18) **4** (395), **6** (80), **7** (10)
11 *Theobroma grandiflorum* (Spreng.) Schum. Sterculiaceae	Manaus/ Manaus	**1a**, **1c**, **2a**, **2b** **6**
12 *Theobroma sylvestre* Mart. Sterculiaceae	Manaus/ Manaus	**1a**, **1c**, **2a**, **2b** **6**

the heterocycle, and this must be different for both systems.

The synthesis of model chromanones was accomplished by Friedel–Crafts reactions of crotonic anhydride [2] on three substrates: 2,4-dihydroxytoluene (**12a**), 2,4-dihydroxybenzaldehyde (**12b**) and 2-hydroxy-4-methoxybenzaldehyde (**12c**). Several previously unreported compounds were thus obtained. In the 60 MHz PMR spectra of the 2-methylchromanones **13a**, **13b**, **13c**, **14** and **15** the protons at C-2 were uniformly represented by an apparent sextet (J = 7 Hz) and the protons at C-3 were represented by a doublet (J = 7 Hz). (Slight secondary splitting of peaks, observed in some cases, is not taken into consideration).

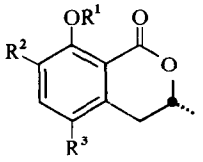
By this criterion, only **1b** could be a 2-methylchromanone. Its methyl ether **1h**, however, shows the very different $OCHCH_2$ PMR pattern, typical of the methyl either **1g** and of the natural compounds **1a**, **1c**–**1f**, **2a**, **2b**. Here the oxymethine is represented by a multiplet and the vicinal methylene by two double doublets. Thus, although two types of spectra are indeed obtained, conformational effects for derivatives of an identical skeleton (**1b** vs **1h**) may obscure the issue.

A further phenomenon which can be attributed to conformation concerns the considerable diamagnetic effect exerted on H-5 (τ 3.60) of **1b**. This, possibly hyperconjugative, effect can be cancelled by modification of the geometry of the heterocycle through interruption of the chelate bridge. Thus, after methylation to **1h**, the H-5 signal appears at the normal frequency (τ 3.04) expected for aromatic protons *para* or *ortho* related to one oxygen function.

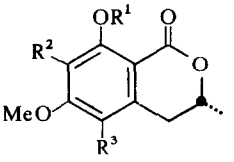
Less subject to conformational than to constitutional causes, MS should solve the problem at hand. Through retro-Diels–Alder cleavages, the isocoumarins (**8**) are expected to loose acetaldehyde, whereas the chromanones are expected to loose propene. Indeed, while loss of 42 mass units leads to the major and often the base peak of the MS of all synthetic chromanones (**13–15**) the molecular ion, which gives the base peak in the spectra of most natural compounds of series **1** and **2**, looses 44 mass units. The structural type **8**, to which consequently all these natural compounds belong, is characterized by loss of 18 mass units (Table 3) which is an additional distinctive MS feature in comparison with type **9**.

The 3-methyl-3,4-dihydroisocoumarin structure for **1a** was confirmed by $NaBH_4$ reduction of its methyl ether **1g** to **16a**, which was characterized by PMR and MS of its diacetate **16b**. Mps, UV, IR, PMR [7] and MS, as well as the negative rotations [8] of **1a** and **1g**, identified **1a** with the known (3*R*)-8-hydroxy-3,5-dimethyl-3,4-dihydroisocoumarin (5-methylmellein). The evidence concerning the vicinality of its two aromatic protons thus leads to the 7-methylmellein structure for **1b**.

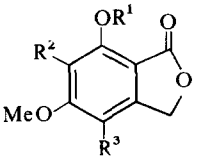
Placement of the substituents at C-5, rather than at C-7, in the formulae for **1c–1f** and **2a** followed three sets of observations: (1) exchange of the Me of **1a** by the CHO of **1c** causes a 1 ppm paramagnetic shift of the H_{eq}-4 PMR signal, and air oxidation of **1c** gives **1d**; (2) **1e** is not a catechol and methylation of **1e** gives **1f**; (3) the PMR of **2a** shows a −0.3 ppm pyridine induced solvent shift [9] for the ArH signal, revealing OH/H vicinality, and a 3.0:2.5 height ratio for the OMe/Me peaks, revealing Me/CH_2 interaction. Placement of the Me rather than other substituents at C-5 in the formulae of **2b** and **3a** was based on the PMR spectrum of **2b** in which the 3.0:2.3 height ratio for the OMe/Me peaks was shifted to 3.0:3.3 by double irradiation at the CH_2 frequency and the PMR spectrum of **3a** in which the 1.1:3.0:2.0 height ratio for the CH_2/OMe/Me peaks was shifted to 2.0:3.0 for CH_2/OMe by double irradiation at the Me frequency.



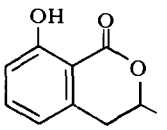
1a $R^1 = R^2 = H$, $R^3 = Me$
1b $R^1 = R^3 = H$, $R^2 = Me$
1c $R^1 = R^2 = H$, $R^3 = CHO$
1d $R^1 = R^2 = H$, $R^3 = CO_2H$
1e $R^1 = R^2 = H$, $R^3 = OH$
1f $R^1 = R^2 = H$, $R^3 = OMe$
1g $R^1 = R^3 = Me$, $R^2 = H$
1h $R^1 = R^2 = Me$, $R^3 = H$



2a $R^1 = R^2 = H$, $R^3 = Me$
2b $R^1 = H$, $R^2 = OMe$, $R^3 = Me$
2c $R^1 = R^2 = R^3 = H$
2d $R^1 = R^3 = H$, $R^2 = OMe$
2e $R^1 = Me$, $R^2 = OMe$, $R^3 = H$



3a $R^1 = H$, $R^2 = CHO$, $R^3 = Me$
3b $R^1 = R^2 = Me$, $R^3 = CO_2Me$



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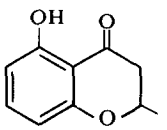

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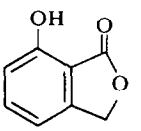

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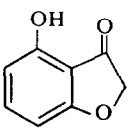

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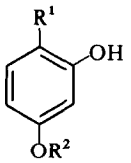
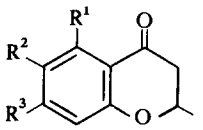
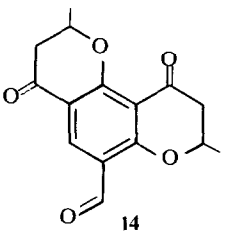


12a $R^1 = Me$, $R^2 = H$
12b $R^1 = CHO$, $R^2 = H$
12c $R^1 = CHO$, $R^2 = Me$
12d $R^1 = CHO$, $R^2 = COCH{=}CHMe$



13a $R^1 = H$, $R^2 = Me$, $R^3 = OH$
13b $R^1 = OH$, $R^2 = CHO$, $R^3 = H$
13c $R^1 = H$, $R^2 = CHO$, $R^3 = OH$



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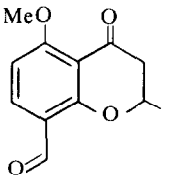

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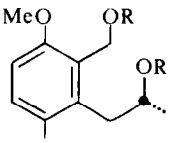

16a R = H
16c R = Ac

Table 2. Friedel–Crafts reactions involving substrate, crotonic anhydride and $AlCl_3$

Substrate	Solvent	Temp (°)	Time (min)	Products (yield %)
12a	ϕNO_2	25	30	**13a** (39)
12b	ϕNO_2	25	30	**13b** (32), **13c** (14), **14** (31)
12b	ϕNO_2	25	60	**13b** (36), **13c** (16), **14** (7)
12b	ϕNO_2	80	30	**13b** (30), **13c** (13)
12b	ϕNO_2	80	60	**13b** (34), **13c** (15)
12b	$\phi NO_2 + CS_2$	25	30	**13b** (27), **13c** (8), **12d** (42)
12b	$\phi NO_2 + CS_2$	80	30	**13b** (57), **13c** (15)
12c	ϕNO_2	25	30	**13c** (21), **15** (57)

Table 3. MS of 3-methyl-3,4-dihydroisocoumarins (**1**, **2**) and of 2-methylchromanones (**13–15**)

		Fragment Ions M−								
	M	15	18	29	15 + 18	42	43	44	28 + 42	28 + 44
1a	99		93	75			43	97		100
1b	100		50	28	30			68		42
1c	100	70	11	20	27		61	8		34
1d	100	20	15	40	45					45
1e	100		68	35						
1f	100	11	67	51	97		15			
1g	85			16	20		20	24		
1h	51	14	12	11	38		19	42		
2a	85		21	12				39		100
2b	28	5		4	8		11			
13a	61	53				100	13		34	
13b	92					40	35		85	
13c	66					100			59	
14	42					20			100	
15	86			32			15		100	

Additional important peaks: **1b**: M-46 (24). **1d**: M-44-45 (10). **1g**: M-46 (98), 145 (98), 132 (35), 104 (100). **1h**: M-46 (90), 145 (91), M-30-44 (47), 104 (100). **2b**: 191 (26), 105 (17), 91 (43), 39 (100). **13b**: M-28 (100). **14**: M-41-42 (50), M-42-42 (11), M-42-42-28 (34). **15**: M-29-42 (35), M-28-43 (35), M-28-28-43 (61).

DISCUSSION

The recent literature reports the occurrences of three further dihydroisocoumarins **2c** (6-methoxymellein), **2d** and **2e** in *Kigelia pinnata* DC. (Bignoniaceae) [8] and of the phthalide **3b** (djalonensin) in *Anthocleista djalonensis* A. Chev. (Loganiaceae) [10]. The stem bark of the latter species is also reported to contain lichexanthone. We have isolated lichexanthone accompanied by physicion twice from higher plants. In the first case [11] the presence of both compounds was subsequently proved to be due to contamination of the plant material (*Licaria puchury-major* (Mart.) Kosterm., Lauraceae) by the lichen *Graphinia confluens* Fée (Graphidiaceae) [12] identified by Dr. Mason E. Hale Jr. In the second case [3] we were not able, *a posteriori*, to secure a fresh sample of the extracted plant material (*Caraipa costata* Spruce *ex* Benth., Guttiferae). This was also true for the wood samples 1, 2, 4–10 (Table 1) described in the present paper. The point to be emphasized, nevertheless, is that all plant material must be thoroughly examined for contaminating organisms prior to extraction, if it is desired to avoid uncertainty concerning the origin of the isolated compounds.

EXPERIMENTAL

Isolation of the compounds. The C_6H_6 extracts of trunk wood samples of the indicated species (Table 1) were submitted to Si gel column chromatography The fractions were purified by TLC on Si gel.

(3R)-*8-Hydroxy-3,5-dimethyl-3,4-dihydroisocoumarin* (**1a**). Mp and lit. [7] mp 126–127° (C_6H_6–C_6H_{14}). $[\alpha]_D^{21}$ −115° ($CHCl_3$) [Found: C, 68.50; H, 6.30 $C_{11}H_{12}O_3$ requires: C, 68.74; H, 6.29%]. UV λ_{max}^{EtOH} nm: 247, 322 (log ε 3.82, 3.63); $\lambda_{max}^{EtOH+AlCl_3}$ nm: 260, 360 (log ε 3.66, 3.51). Gibbs test: negative. IR ν_{max}^{KBr} cm^{-1}: 3400, 1660, 1610, 1230, 1200, 1130, 1060. PMR ($CDCl_3$, 100 MHz, τ): −1.02 (*s*, OH), 2.75 (*d*, *J* = 8.0 Hz, H-6), 3.16 (*d*, *J* = 8.0 Hz, H-7), 5.1–5.5 (*m*, H-3), 7.00 (*dd*, *J* = 16.0, 4.0 Hz, H_{eq}-4), 7.28 (*dd*, *J* = 16.0, 10.5 Hz, H_{ax}-4), 7.79 (*s*, Me-5), 8.42 (*d*, *J* = 6.0 Hz, Me-3). ORD (*c* 1 mg/10 ml, MeOH, 220–360 nm): $[\phi]_{345}$ −250, $[\phi]_{315}^{pk}$ −100, $[\phi]_{271}^{tr}$ −1050, $[\phi]_{261}$ 0, $[\phi]_{250}^{pk}$ +17650, $[\phi]_{238}$ 0, $[\phi]_{232}^{tr}$ −400, $[\phi]_{225}$ 0. Methyl ether (**1g**): mp and lit. [7] mp 92–93°, $[\alpha]_D^{20}$ −110° ($CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1725, 1270, 1120, 830. PMR ($CDCl_3$, 60 MHz, τ): 2.82 (*d*, *J* = 8.5 Hz, H-6), 3.28 (*d*, *J* = 8.5 Hz, H-7), 5.4–5.9 (*m*, H-3), 6.23 (*s*, OMe), 7.15 (*dd*, *J* = 16.0, 4.0 Hz, H_{eq}-4), 7.53 (*dd*, *J* = 16.0, 10.5 Hz, H_{ax}-4), 7.80 (*s*, Me-5), 8.50 (*d*, *J* = 6.0 Hz, Me-3).

(3R)-*8-Hydroxy-3,7-dimethyl-3,4-dihydroisocoumarin* (**1b**). Mp 100–102° (Et_2O–C_6H_{14}). $[\alpha]_D^{21°}$ −78° ($CHCl_3$) [Found: C, 68.65; H, 6.35. $C_{11}H_{12}O_3$ requires: C, 68.74; H, 6.29%] UV λ_{max}^{EtOH} nm: 250, 320 (log ε 3.85, 3.60); IR $\nu_{max}^{EtOH+AlCl_3}$ nm: 264, 360 (log ε 3.70, 3.49). IR ν_{max}^{KBr} cm^{-1}: 2965 *br*, 1665, 1625, 1460, 1425. PMR ($CDCl_3$, 60 MHz, τ): −1.20 (*s*, OH), 2.85 (*d*, *J* = 7.5 Hz, H-6), 3.60 (*d*, *J* = 7.5 Hz, H-5), 5.39 (apparent *q*, *J* = 7.0 Hz, H-3), 7.20 (*d*, *J* = 7.0 Hz, 2H-4), 7.81 (*s*, Me-7), 8.51 (*d*, *J* = 7.0 Hz, Me-3). Methyl ether (**1h**). IR ν_{max}^{KBr} cm^{-1}: 1727, 1610, 1265, 1128, 1070. PMR ($CDCl_3$, 60 MHz, τ): 2.58 (*d*, *J* = 8.0 Hz, H-6), 3.04 (*d*, *J* = 8.0 Hz, H-5), 5.38 (*m*, H-3), 6.06 (*s*, OMe), 7.20 (*m*, 2H-4), 7.66 (*s*, Me-7), 8.50 (*d*, *J* = 7.0 Hz, Me-3).

(3R)-*5-Formyl-8-hydroxy-3-methyl-3,4-dihydroisocoumarin* (**1c**). Mp 115–117° (C_6H_6) [Found: C, 63.95; H, 4.78 $C_{11}H_{10}O_4$ requires: C, 64.07; H, 4.89%]. UV λ_{max}^{MeOH} nm: 237, 277, 316 (log ε 4.34, 3.96, 3.61); $\lambda_{max}^{MeOH+AlCl_3}$ nm: 247, 350 (log ε 4.36, 4.00, 3.71). IR ν_{max}^{KBr} cm^{-1}: 3400, 1665 br, 1240, 1185, 1130. PMR ($CDCl_3$, 60 MHz, τ): −2.03 (*s*, OH), −0.01 (*s*, CHO), 2.05 (*d*, *J* = 8.0 Hz, H-6), 2.93 (*d*, *J* = 8.0 Hz, H-7), 5.0–5.5 (*m*, H-3), 6.00 (*dd*, *J* = 18.0, 4.0 Hz, H_{eq}-4), 6.96 (*dd*, *J* = 18.0, 10.0 Hz, H_{ax}-4), 8.40 (*d*, *J* = 6.0, Me-3). ORD (*c* 1 mg/10 ml, MeOH, 220–360 nm): $[\phi]_{345}$ −300, $[\phi]^{pk}$ −100, $[\phi]_{292}^{tr}$ −550, $[\phi]_{284}$ 0, $[\phi]_{276}^{pk}$ +1300, $[\phi]_{268}$ 0 [illegible] −1100, $[\phi]_{255}$ 0

(3R)-*5-Carboxy-8-hydroxy-3-methyl-3,4-dihydroisocoumarin* (**1d**). Mp 247–249° (EtOH) [Found: C, 59.31; H, 4.49. $C_{11}H_{10}O_5$ requires: C, 59.46; H, 4.54%]. UV λ_{max}^{EtOH} nm: 222, 242, 322 (log ε 4.46, 3.97, 3.94); $\lambda_{max}^{EtOH+AlCl_3}$ nm: 230, 247, 312 (log ε 4.44, 3.99, 4.25); IR ν_{max}^{KBr} cm^{-1}: 3200, 1690, 1660, 1580, 1460, 1380, 980, 830. Acetate, mp 166–168° (EtOH). PMR ($CDCl_3$, 60 MHz, τ): 1.67 (*d*, *J* = 8.0 Hz, H-6), 2.81 (*d*, *J* = 8.0 Hz, H-7), 5.2–5.6 (*m*, H-3), 6.6–7.2 (*m*, 2H-4), 7.61 (*s*, OAc), 8.46 (*d*, *J* = 6.0 Hz, Me-3)

(3R)-5,8-Dihydroxy-3-methyl-3,4-dihydroisocoumarin (**1e**). Mp 198–200° (C_6H_6) [Found: C, 61.70; H, 5.10. $C_{10}H_{10}O_4$ requires: C, 61.85; H, 5.19%]. UV λ_{max}^{EtOH} nm: 222, 250, 350 (log ε 4.28, 3.78, 3.65); $\lambda_{max}^{EtOH+AlCl_3}$ nm: 222, 252, 352 (log ε 4.29, 3.84, 3.60); no H_3BO_3 + NaOAc shift. IR ν_{max}^{KBr} cm^{-1}: 3400, 1645, 1590, 1480, 1050, 830. Acetate, oil, IR ν_{max}^{film} cm^{-1}: 1760, 1720, 1610, 1480, 1260, 830. PMR ($CDCl_3$, 60 MHz, τ) 2.75 (*d*, *J* = 8.0 Hz, H-6), 2.96 (*d*, *J* = 8.0 Hz, H-7), 5.2–5.6 (*m*, H-3), 7.1–7.5 (*m*, 2H-4), 7.67 (*s*, 2OAc), 8.56 (*d*, *J* = 6.0 Hz, Me-3).

(3R)-8-Hydroxy-5-methoxy-3-methyl-3,4-dihydroisocoumarin (**1f**). Mp 71–72° (Et_2O–C_6H_{14}), $[\alpha]_D^{21°}$ −116° ($CHCl_3$) [Found: C, 63.55; H, 5.75. $C_{11}H_{12}O_4$ requires: C, 63.45; H, 5.81%]. UV [λ_{max}^{EtOH} nm: 240 inf., 343 (log ε 3.68, 3.56); $\lambda_{max}^{EtOH+AlCl_3}$ nm: 265, 385 (log ε 3.78, 3.62). IR ν_{max}^{KBr} cm^{-1}: 3140, 1670, 1608, 1585, 1270, 1225, 1180, 1122, 1060. PMR ($CDCl_3$, 60 MHz, τ): −0.56 (*s*, OH), 2.90 (*d*, *J* = 9.0 Hz, H-6), 3.13 (*d*, *J* = 9.0 Hz, H-7), 5.2–5.5 (*m*, H-3), 6.19 (*s*, OMe), 6.77 (*dd*, *J* = 16.0, 4.0 Hz, H_{eq}-4), 7.40 (*dd*, *J* = 16.0, 10.0 Hz, H_{ax}-4), 8.45 (*d*, *J* = 6.0 Hz, Me-3).

(3R)-8-Hydroxy-6-methoxy-3,5-dimethyl-3,4-dihydroisocoumarin (**2a**). Mp 118–119° (C_6H_{14}), $[\alpha]_D^{21°}$ −98° ($CHCl_3$) [Found: C, 64.70; H, 6.39. $C_{12}H_{14}O_4$ requires: C, 64.85; H, 6.35%]. UV λ_{max}^{EtOH} nm: 267, 310 (log ε 4.07, 3.78); $\lambda_{max}^{EtOH+AlCl_3}$ nm: 280, 342 (log ε 4.07, 3.72). IR ν_{max}^{KBr} cm^{-1}: 2970 br, 1660, 1620, 1580, 1470, 1440. PMR ($CDCl_3$, 60 MHz, τ): −1.20 (*s*, OH), 3.80 (*s*, H-7), 5.50 (*m*, H-3), 6.16 (*s*, OMe), 7.15 (*dd*, *J* = 16.5, 5.0 Hz, H_{eq}-4), 7.40 (*dd*, *J* = 16.5, 11.0 Hz, H_{ax}-4), 8.02 (*s*, Me-5), 8.49 (*d*, *J* = 7.0 Hz, Me-3). PMR (C_5D_5N, 60 MHz, τ): 3.50 (*s*, H-7), 5.50 (*m*, H-3), 6.30 (*s*, OMe), 7.07 (*dd*, *J* = 5.0, 16.5 Hz, H_{eq}-4), 7.66 (*dd*, *J* = 11.0, 16.5 Hz, H_{ax}-4), 8.02 (*s*, Me-5), 8.67 (*d*, *J* = 7 Hz, Me-3).

(3R)-8-Hydroxy-6,7-dimethoxy-3,5-dimethyl-3,4-dihydroisocoumarin (**2b**). Bp 110–112° (0.15 mm Hg) [Found: C, 61.75; H, 6.40. $C_{13}H_{16}O_5$ requires: C, 61.90; H, 6.39%]. UV λ_{max}^{EtOH} nm: 266, 319 (log ε 3.94, 3.55). IR ν_{max}^{film} cm^{-1}: 2900 br, 1667, 1361, 1212, 1124, 1055, 961, 945, 836, 805. PMR ($CDCl_3$, 60 MHz, τ): −1.90 (*s*, OH), 5.15–5.60 (*m*, H-3), 6.04 (*s*, OMe), 6.10 (*s*, OMe), 6.8–7.3 (*m*, 2H-4), 7.92 (*s*, Me-5), 8.47 (*d*, *J* = 6.0 Hz, Me-3). PMR (C_5D_5N, 60 MHz, τ); 4.8–5.6 (*m*, H-3), 6.05 (*s*, 2 OMe), 6.9–7.6 (*m*, 2H-4), 7.95 (*s*, Me-5), 8.64 (*d*, *J* = 6.0 Hz, Me-3).

6-Formyl-7-hydroxy-5-methoxy-4-methylphthalide (**3a**). Mp 161–163° [Found: C, 59.60; H, 4.45. $C_{11}H_{10}O_5$ requires: C, 59.46; H, 4.54%]. UV λ_{max}^{EtOH} nm: 265, 299, 368 (log ε 4.15, 3.89, 3.46); $\lambda_{max}^{EtOH+AlCl_3}$ nm: 263, 306, 368 (log ε 4.15, 3.72, 3.49); no NaOH shift. IR ν_{max}^{KBr} cm^{-1}: 3410, 1742, 1706, 1647, 1615, 1580, 1350, 1294, 1208, 780. PMR ($CDCl_3$, 60 MHz, τ): −2.07 (*s*, OH), 0.10 (*s*, CHO), 4.50 ($ArCH_2OCO$), 5.80 (*s*, OMe), 7.83 (*s*, ArMe). MS *m/e* (rel. int.): 222 (45) M, 204 (31), 193 (35), 192 (64), 176 (66), 164 (56), 148 (59), 135 (21), 120 (24), 107 (21). Methyl ether, ν_{max} cm^{-1}: 1772.

Friedel–Crafts reactions. To a soln of substrate (0.02 mol) and dry $AlCl_3$ (0.04 mol) in solvent (40 ml) were added portionwise crotonic anhydride (0.02 mol) and further $AlCl_3$ (0.06 mol) with shaking [2] during the indicated time and temp (Table 3). The mixture was kept at room temp. (48–72 hr) and poured into iced 6N HCl (100 ml). The aq. layer was extracted with Et_2O (3 × 60 ml). The organic layer and the Et_2O solns were combined and submitted to vapour entrainment. The residue was separated into products by Si gel column chromatography.

4-O-Crotonyl-2-hydroxybenzaldehyde (**12d**). Mp 32–34° (petrol) [Found: C, 63.89; H, 4.75. $C_{11}H_{10}O_4$ requires: 64.07; H, 4.89%]. UV λ_{max}^{EtOH} nm: 262, 322 (log ε 4.25, 3.66); $\lambda_{max}^{EtOH+AlCl_3}$ nm: 234 inf., 276, 375 (log ε 4.34, 4.25, 3.57). Gibbs test: positive. IR ν_{max}^{KBr} cm^{-1}: 3450, 1740, 1665, 1625, 1210, 1160, 1120, 1000. PMR ($CDCl_3$, 60 MHz, τ): −1.48 (*s*, OH), 0.10 (*s*, CHO), 2.40 (*d*, *J* = 8.7 Hz, H-6), 2.70 (*dq*, *J* = 14.7, 6.7 Hz, CH=), 3.10 (*dd*, *J* = 8.7, 2.0 Hz, H-5), 3.10 (*d*, *J* = 2.0 Hz, H-3), 3.93 (*dq*, *J* = 14.7, 2.0 Hz, CH=), 8.00 (*dd*, *J* = 7.0, 2.0 Hz, Me).

7-Hydroxy-2,6-dimethylchromanone (**13a**). Mp 202–204° (C_6H_6), subl. 160° [Found: C, 68.95; H, 6.31. $C_{11}H_{12}O_3$ requires: C, 68.74; H, 6.29%]. UV λ_{max}^{EtOH} nm: 237, 279, 329 (log ε 3.68, 3.72, 3.59); no $AlCl_3$-shift. IR ν_{max}^{KBr} cm^{-1}: 3300, 1660, 1600, 1285, 1175. PMR ($CHCl_3$, 100 MHz, τ): 2.33 (*s*, H-5), 3.64 (*s*, H-8), 5.43 (*s*, *J* = 7.0 Hz, H-2), 7.38 (*d*, *J* = 7.0 Hz, 2 H-3), 7.80 (*s*, Me-6), 8.52 (*d*, *J* = 6.0 Hz, Me-2).

6-Formyl-5-hydroxy-2-methylchromanone (**13b**). Mp 111–113° (C_6H_6) [Found: C, 64.18; H, 4.79. $C_{11}H_{10}O_4$ requires: C, 64.07; 4.89%]. UV λ_{max}^{EtOH} nm: 242, 267, 284 inf., 350 (log ε 3.78, 3.72, 3.61, 3.17); $\lambda_{max}^{EtOH+AlCl_3}$ nm: 243, 285, 303 inf., 400 (log ε 3.73, 3.69, 3.54, 3.18). Gibbs test: positive. IR ν_{max}^{KBr} cm^{-1}: 3400, 1680, 1630, 1600, 1250, 1240, 1200, 1185. PMR ($CDCl_3$, 100 MHz, τ): −2.44 (*s*, OH), −0.30 (*s*, CHO), 2.06 (*d*, *J* = 8.0 Hz, H-7), 3.51 (*d*, *J* = 8.0 Hz, H-8), 5.33 (sec. split *tq*, *J* = 7.5 Hz, H-2), 7.24 (sec. split *d*, *J* = 7.5 Hz, 2 H-3), 8.42 (*d*, *J* = 6.0 Hz, Me-2).

6-Formyl-7-hydroxy-2-methylchromanone (**13c**). Mp 159–161° (MeOH), subl. 125° [Found: C, 63.82; H, 4.71. $C_{11}H_{10}O_4$ requires: C, 64.07; H, 4.89%]. UV λ_{max}^{EtOH} nm: 258, 285, 312, 370 (log ε 4.25, 3.99, 3.98, 3.61); $\lambda_{max}^{EtOH+AlCl_3}$ nm: 270, 360 (log ε 4.43, 3.31). IR ν_{max}^{KBr} cm^{-1}: 3020, 1690, 1640, 1190. PMR ($CDCl_3$, 60 MHz, τ): −1.48 (*s*, OH), 0.22 (*s*, CHO), 1.81 (*s*, H-5), 3.56 (*s*, H-8), 5.14 (sec. split *tq*, *J* = 7.5 Hz, H-2), 7.14 (sec. split *d*, *J* = 7.5 Hz, 2 H-3), 8.46 (*d*, *J* = 6.0 Hz, Me-2).

9-Formyl-3,7-dimethyl-1,2,3,4,5,6,7,8-octahydro-1,5-dioxo-4,8-dioxaphenanthrene (**14**). Mp 190–192° (C_6H_6) [Found: C, 65.29; H, 5.08. $C_{15}H_{14}O_5$ requires: C, 65.69; H, 5.15%]. UV λ_{max}^{EtOH} nm: 250, 288 inf., 346 (log ε 4.57, 4.14, 3.87); no $AlCl_3$, shift. IR ν_{max}^{KBr} cm^{-1}: 1690, 1670, 1220, 1190, 1080. PMR ($CDCl_3$, 60 MHz, τ): −0.27 (*s*, CHO), 1.47 (*s*, H-10), 5.0–5.5 (*m*, H-2, H-6), 7.13 (*d*, *J* = 8.0 Hz, H-3 or H-7), 7.14 (*d*, *J* = 8.0 Hz, H-7 or H-3), 8.40 (*d*, *J* = 6.0 Hz, Me-2, Me-6).

8-Formyl-5-methoxy-2-methylchromanone (**15**). Mp 151–152° (C_6H_6) [Found: C, 65.33; H, 5.45. $C_{12}H_{12}O_4$ requires: C, 65.45; H, 5.49%]. UV λ_{max}^{EtOH} nm: 245, 260, 282 inf., 340 (log ε 4.00, 4.00, 3.76, 3.49). PMR ($CDCl_3$, 100 MHz, τ): −0.28 (*s*, CHO), 2.09 (*d*, *J* = 8.0 Hz, H-7), 3.40 (*d*, *J* = 8.0 Hz, H-6), 5.25 (*tq*, *J* = 8.0 Hz, H-2), 6.02 (*s*, OMe-5), 7.30 (*d*, *J* = 8.0 Hz, 2 H-3), 8.43 (*d*, *J* = 6.0 Hz, Me-2).

Reduction of 5-methylmellein methyl ether. **2g** (50 mg), reduced with $NaBH_4$ according to ref. [14], gave **16a** (35 mg).

(2'S)-2-Hydroxymethyl-3-(2'-hydroxy-n-propyl)-1-methoxy-4-methylbenzene (**16a**). Mp 109–110° (C_6H_{14}–Et_2O), $[\alpha]_D^{25°}$ −38° ($CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3250, 1585, 1500, 1260, 1115, 1090, 1002, 935, 820. PMR ($CDCl_3$, D_2O, 60 MHz, τ): 2.93 (*d*, *J* = 9.0 Hz, H-5), 3.33 (*d*, *J* = 9.0 Hz, H-6), 5.08 (*d*, *J* = 11.0 Hz, CH-2), 5.48 (*d*, *J* = 11.0 Hz, CH-2), 6.13 (*m*, H-2'), 6.20 (*s*, OMe-1), 7.18 (*d*, *J* = 6.0 Hz, 2H-1'), 7.77 (*s*, Me-4), 8.73 (*d*, *J* = 7.0 Hz, 3H-3'). MS *m/e* (rel. int.): 210 (1) $C_{12}H_{18}O_3$ requires: 210, 148 (100), 118 (15), 117 (15). Diacetate (**16b**), oil, $[\alpha]_D^{25°}$ −9.0 ($CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1740, 1250, 1028, 820. PMR (CCl_4, 60 MHz, τ): 3.03 (*d*, *J* = 9.0 Hz, H-5), 3.50 (*d*, *J* = 9.0 Hz, H-6), 4.90 (*s*, CH_2-2), 5.03 (*m*, H-2'), 6.27 (*s*, OMe-1), 7.10 (*d*, *J* = 8.5 Hz, H-1'), 7.17 (*d*, *J* = 8.5 Hz, H-1'), 7.70 (*s*, Me-4), 8.03 (*s*, OAc), 8.13 (*s*, OAc), 8.78 (*d*, *J* = 6.5 Hz, 3 H-3'). MS *m/e* (rel. int.): 294 (10) M, 234 (11), 191 (45), 174 (100), 159 (35), 148 (96), 118 (22), 117 (16), 105 (12).

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