A Novel Synthesis of Precocenes. Efficient Synthesis and Regioselective *O*-Alkylation of Dihydroxy-2,2-dimethyl-4-chromanones [1]

Tibor Timár*

Alkaloida Chemical Company,
Tiszavasvári, H-4440, Hungary

J. Csaba Jászberényi

Research Group of Antibiotics of the Hungarian
Academy of Sciences, L. Kossuth University,
Debrecen, H-4010, Hungary

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The reactions of trihydroxybenzenes **1a-c** and 3-methylbut-2-enoic acid (**2**) in a zinc chloride/water/phosphoryl chloride system afford either the new trihydroxyphenylbutenone derivatives **3b,c** or dihydroxy-2,2-dimethyl-4-chromanones **4a-c** in good yields. Compounds **3b,c** can be cyclized in high yields to **4b,c** in 5% sodium hydroxide solution. Regioselective *O*-alkylation of **4a-c** leads to **5a-f** in good yields. *O*-Alkylation of **5a-f**, followed by reduction and dehydration, results in the formation of precocene 3 (**7d**) and its regioisomer **7a-c,e,f**. Methylation of **4a-c** gives **6g-i**. Subsequent reduction and dehydration affords precocene 2 (**7h**) and its regioisomers **7g,i**.

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Precocenes **7d,h** are proallatocidins [2]. They are bioactivated in the juvenile hormone producing organ (*corpora allata*) of susceptible insects [2,3]. As a consequence of this attractive biological property, several synthetic methods have been reported [4-7]. Due to the relative complexity but only moderate yields, not all of these procedures are suitable for the synthesis of precocene 2 (**7h**), precocene 3 (**7d**) (which is the most active derivative) and their regioisomers. Dihydroxy-2,2-dimethyl-4-chromanones **4a-c** appear to be ideal intermediates, provided that a high-yield method is available for their synthesis. Regioselective alkylation is needed to obtain **7d**, its regioisomers and other analogues. The available methods are summarized in Table 1.

5,7-Dihydroxychromanone (**4a**) has been reported to be obtained in 39-90% yield, 6,7-dihydroxychromanone (**4b**) in 30-42% yield, and 7,8-dihydroxychromanone (**4c**) in 14-30% yield (Table 1). The low reported yields for **4b** and **4c** prompted us to find an alternative method that is also suitable for the synthesis of **4a**. The method with the highest reported yield for **4a** (90%, Lit [13]) was selected as a likely possibility. However, on repeating the reported procedure on the same scale in several experiments, we found that it gave only a mixture of products in an overall yield of up to 60%.

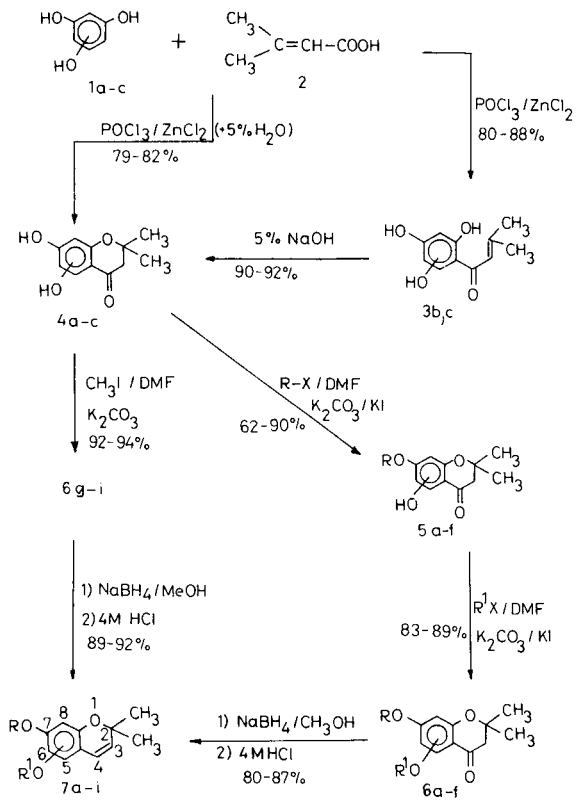
Tlc revealed that this mixture does contain **4a**, but this compound was isolated from this mixture at best in 30-40% yield (with difficulty). The same method applied to

Table 1

Reported Reactions of Trihydroxybenzenes **1a-c** and 3-Methylbut-2-enoic acid (**2**)

No.	Reagent	Yield (%)	Method of characterisation			Reference
			mp (°)	microanalysis	other	
4a	$AlCl_3/C_6H_5-NO_2$	72	198	+	–	[8]
	$SbCl_3$	39	196-197	+	–	[9]
	$BF_3/(C_2H_5)_2O$	65	198	+	–	[10]
	$BF_3/C_6H_5-NO_2$	82	194-195	+	–	[11]
	$ZnCl_2/POCl_3$	67	197-198	+	–	[12]
	$AlCl_3/POCl_3$	90	197-198	–	–	[13]
4b	$BF_3/(C_2H_5)_2O$	30 [a]	208	+	–	[10]
	CH_3SO_3H/P_2O_5	42 [a]	207-209	+	ir, pmr	[14]
4c	$AlCl_3/C_6H_5-NO_2$	24	142-143	+	–	[15]
	$ZnCl_2/POCl_3$	no data	142	–	–	[12]
	PPA [b]	14	138-141	–	ir, pmr, ms	[16]
	$AlCl_3/POCl_3$	30	142-143	–	–	[13]

[a] 1,2,4-Triacetoxybenzene was used instead of 1,2,4-trihydroxybenzene. [b] Polyphosphoric acid.



Scheme

the synthesis of **4c** (reported yield 30%) gave a product in the reported yield. However, the ^{1}H nmr spectrum demonstrated that this compound is not **4c** as claimed [13] but **3c**. The very similar melting points (136-138° for **3c** and 142-143° for **4c**) may account for this mistake. Use of this method in attempts to prepare **4b** gave only a mixture of products (containing **4b**). Because of the problems encountered during use of the aluminum chloride/phosphoryl chloride method [13], we tried other Lewis acids. From the chosen reagents (aluminum chloride, zinc chloride, ferric chloride, stannic chloride, antimony pentachloride, titanium(IV) chloride) in phosphoryl chloride, we found that the phosphoryl chloride/zinc chloride system was the best. An optimum amount of water (5%, normally present in unfused, commercial zinc chloride) resulted in a 10 to 100-fold decrease in reaction time compared to that for the anhydrous phosphoryl chloride/zinc chloride system [12]. It is worth noting, however, that a higher amount of water facilitates the formation of by-products, thereby reducing the yields of **4a-c** and complicating the work-up. Use of the fused zinc chloride/phosphoryl chloride system enabled us to isolate **3b,c** which were then cyclized in 5% aqueous sodium hydroxide solution to **4b,c** (Scheme).

Regioselective alkylation with either methyl or ethyl halides resulted in the formation of the corresponding 7-*O*-alkylated monohydroxy intermediates **5a-f** in high yields (Table 3). The efficient synthesis of these intermedi-

Table 2

Reaction of Trihydroxybenzenes **1a-c** and 3-Methylbut-2-enoic acid (**2**)

Product	Reaction time (hour)	Yield (%)	mp (°)	IR (KBr) ν (cm^{-1})	^{1}H NMR (DMSO-d$_6$) δ (ppm)	MS m/e (%)
3b	2	88	162-164	3396, 3277, 1636, 1439, 1261, 1233, 848, 796	2.00 (d, 3H, J = 1Hz, CH_3), 2.12 (d, 3H, J = 1Hz, CH_3), 6.32 (s, 1H, 3'-H), 6.75 (m, 1H, 2-H), 7.22 (s, 1H, 6'-H), 8.60 (broad, 1H, OH), 10.20 (broad, 1H, OH), 12.8 (s, 1H, 2'-OH)	208 (M$^+$, 25), 193 (100), 153 (53), 152 (31)
3c	4	80	136-138	3433, 2975, 1631, 1503, 1449, 1278, 1006, 804, 709	2.01 (d, 3H, J = 1 Hz, CH_3), 2.15 (d, 3H, J = 1 Hz, CH_3), 6.41 (d, 1H, J = 10 Hz, 5'-H), 6.92 (m, 1H, 2-H), 7.42 (d, 1H, J = 10 Hz, 6'-H), 8.60 (broad, 1H, OH), 10.00 (broad, 1H, OH), 13.30 (s, 1H, 2'-OH)	208 (M$^+$, 22), 193 (100), 153 (32), 152 (33)
4a	3	82	198-199 [a]	3160, 3000, 1650, 1510, 1300, 1200, 1170, 1090, 880, 840	1.45 (s, 6H, 2CH_3), 2.71 (s, 2H, CH_2), 5.92 (m, 2H, ArH), 9.47 (broad, 1H, OH), 12.10 (s, 1H, 5-OH)	208 (M$^+$, 44), 193 (100), 153 (64), 152 (32), 124 (31)
4b	3	79	208-209 [a]	3520, 1656, 1520, 1275, 1165, 900, 880	1.35 (s, 6H, 2CH_3), 2.62 (s, 2H, CH_2), 6.27 (s, 1H, 8-H), 7.05 (s, 1H, 5-H), 8.00 (broad, 1H, OH), 8.50 (broad, 1H, OH)	208 (M$^+$, 60), 193 (100), 153 (95), 152 (72), 124 (12)
4c	5	80	142-143 [a]	3500, 3400, 2995, 1670, 1607, 1465, 1330, 1180, 1040, 950, 795	1.37 (s, 6H, 2CH_3), 2.57 (s, 2H, CH_2), 6.32 (d, 1H, J = 10 Hz, 6-H), 7.07 (d, 1H, J = 10 Hz, 5-H), 8.20 (broad, 2H, OH)	208 (M$^+$, 56), 193 (60), 153 (85), 152 (100), 124 (22)

[a] Lit melting points for **4a-c** are in Table 1.

Table 3

7-*O*-Alkylated-monohydroxy-2,2-dimethyl-4-chromanones **5a-f** Prepared

No.	R	Position of OH	Reaction time (hour) [a]	Yield (%) [b]	mp (°)	Molecular formula or mp (°) reported	IR (KBr) ν (cm^{-1})	^1H NMR (deuteriochloroform) δ (ppm)	MS m/e (%)
5a	CH_3	5	5	90	69-70	48-49 [17] 65-66 [18] 61-64 [19]	3424, 2971, 1643	1.47 (s, 6H, $2CH_3$), 2.71 (s, 2H, CH_2), 3.81 (s, 3H, CH_3O), 5.95 (d, 1H, J = 2 Hz, ArH), 6.03 (d, 1H, J = 2 Hz, ArH), 12.2 (s, 1H, 5-OH)	222 (M^+, 40), 207 (100), 167 (62), 166 (25), 138 (28)
5b	C_2H_5	5	6	82	73-75	$C_{13}H_{16}O_4$	3432, 2979, 1631	1.40 (t, 3H, J = 7 Hz, CH_3CH_2O), 1.46 (s, 6H, $2CH_3$), 2.68 (s, 2H, CH_2), 4.03 (q, 2H, J = 7 Hz, CH_3CH_2O), 5.92 (d, 1H, J = 2 Hz, ArH), 6.00 (d, J = 2 Hz, ArH), 12.01 (s, 1H, 5-OH)	236 (M^+, 56), 221 (100), 193 (26), 181 (43), 153 (27)
5c	CH_3	6	1	85	143-144	98-100 [14] 135-136 [20] 150-151 [16]	3400 2960 1670	1.45 (s, 6H, $2CH_3$), 2.66 (s, 2H, CH_2), 3.91 (s, 3H, CH_3O), 5.41 (s, 1H, 6-OH), 6.42 (s, 1H, 8-H), 7.35 (s, 1H, 5-H)	222 (M^+, 69), 207 (100), 167 (92) 166 (75), 123 (27)
5d	C_2H_5	6	2	80	129-131	$C_{13}H_{16}O_4$	3570, 2980, 1675,	1.45 (s, 6H, $2CH_3$), 1.51 (t, 3H, J = 7 Hz, CH_3CH_2O), 2.67 (s, 2H, CH_2), 4.11 (q, 2H, J = 7 Hz, CH_3CH_2O), 5.35 (s, 1H, 6-OH), 6.37 (s, 1H, 8-H), 7.36 (s, 1H, 5-H)	236 (M^+, 66), 221 (100), 193 (29), 180 (71), 153 (52)
5e	CH_3	8	4	64	78-80	$C_{12}H_{14}O_4$	3180, 2970, 1670,	1.51 (s, 6H, $2CH_3$), 2.72 (s, 2H, CH_2), 3.95 (s, 3H, CH_3O), 6.02 (broad, 1H, 8-OH), 6.62 (d, 1H, J = 10 Hz, 6-H), 7.47 (d, 1H, J = 10 Hz, 5-H)	222 (M^+, 65), 207 (92), 167 (100), 166 (42), 138 (68)
5f	C_2H_5	8	7	62	141-143	$C_{13}H_{16}O_4$	3464, 2975, 1690	1.46 (t, 3H, J = 7 Hz, CH_3CH_2O), 1.52 (s, 6H, $2CH_3$), 2.72 (s, 2H, CH_2), 4.21 (q, 2H, J = 7 Hz, CH_3CH_2O), 5.48 (s, 1H, 8-OH), 6.58 (d, 1H, J = 10 Hz, 6-H), 7.45 (d, 1H, J = 10 Hz, 5-H)	236 (M^+, 47), 221 (60), 181 (67), 152 (100), 123 (32)

[a] Averaged times, based on the gc monitoring of the reaction. [b] Yield of recrystallized compound (from ethanol).

ates enabled us to obtain precocene 3 (**7d**) and its regioisomers **7a-c,e,f** in high overall yields (Table 5). Precocene 2 (**7h**) and its regioisomers **7g,i** were also obtained *via* the route **4a-c** → **6a-i** → **7g-i**.

The efficiency and high yields of the processes thus developed for the synthesis of the dihydroxychromanones **4a-c** and the monoalkylated derivatives **5a-f** made it possible to obtain a wide range of analogues of the natural bioactive precocenes, these are of potential agricultural use [22].

EXPERIMENTAL

Trihydroxybenzenes and 3-methylbut-2-enoic acid were purchased from Aldrich Chemical Co. Methyl iodide and ethyl bromide were obtained from EGA. Phosphoryl chloride was of Merck-Schuchardt. Aluminum chloride was used either as purchased or freshly resublimed without causing any change in the outcome of the reactions. Solvents were purchased from Reanal (Hungary). Melting points were determined on a PHMK hot plate melting point apparatus and are uncorrected. Infrared spectra were recorded in potassium bromide pellets or neat films on a Perkin-Elmer 283B instrument. Mass Spectra were obtained on a VG 7035 instrument in the EI mode (70 eV, direct inlet). The ^1H nmr spectra were obtained at ambient temperature on a Bruker WP-200 SY instrument at 200 MHz. The ^{13}C nmr spectra were recorded on the same spectrometer at 50.3 MHz. A Fractovap 2300 chromatograph (Carlo-Erba) was used for gc analysis. Microanalysis data (L. Kossuth University, Debrecen, Hungary) are summarized in Table 7.

1-(2',4',5'-trihydroxyphenyl)-3-methyl-1-oxo-2-butene (**3b**).

Typical Procedure.

To a stirred mixture of phosphoryl chloride (1352 g, 800 ml, 8.81 moles), and 3-methylbut-2-enoic acid (**2**, 100.2 g, 1 mole), fused zinc chloride (200 g, 1.47 moles) and hydroxyhydroquinone (**1b**, 126.1 g, 1 mole) were added. The mixtue was stirred at 25° for 2 hours, and then poured onto crushed ice (5000 g). The separated solid was filtered, washed with water and dried. The crude product **3b** thus obtained, 183.2 g (88%) was sufficiently pure for use in the following reaction step. It can be purified by recrystallization from ethanol/water, mp 162-164°. Other data are given in Table 2.

6,7-Dihydroxy-2,2-dimethyl-4-chromanone (**4b**).

Table 4

Dialkoxy-2,2-dimethyl-4-chromanones **6a-i** Prepared

No.	R	R^1	Position of OR^1	Reaction time (hour)	Yield (%) [a]	mp (°)	IR (KBr) ν (cm^{-1})	^1H NMR (deuteriochloroform) δ (ppm)	MS m/e (%)
6a	CH_3	C_2H_5	5	50	89	60-62	1678	1.45 (s, 6H, $2CH_3$), 1.51 (t, 3H, J = 7 Hz, CH_3CH_2O), 2.63 (s, 2H, CH_2), 3.82 (s, 3H, CH_3O), 4.07 (q, 2H, J = 7 Hz, CH_3CH_2O), 6.01 (m, 2H, ArH)	250 (M^+, 87), 235 (40), 221 (100)
6b	C_2H_5	CH_3	5	40	84	147-148	1674	1.46 (s, 6H, $2CH_3$, + t, 3H, J = 7 Hz, CH_3CH_2O, 2.66 (s, 2H, CH_2), 3.91 (s, 3H, CH_3O), 4.06 (q, 2H, J = 7 Hz, CH_3CH_2O), 6.03 (m, 2H, ArH)	250 (M^+, 10), 235 (85), 221 (100)
6c	CH_3	C_2H_5	6	12	85	88-90	1680	1.45 (s, 6H, $2CH_3$, + t, 3H, J = 7 Hz, CH_3CH_2O), 2.67 (s, 2H, CH_2), 3.90 (s, 3H, CH_3O), 4.11 (q, 2H, J = 7 Hz, CH_3CH_2O), 6.40 (s, 1H, 8-H), 7.27 (s, 1H, 5-H)	250 (M^+, 83), 235 (100)
6d	C_2H_5	CH_3	6	15	88	124-126	1675	1.45 (s, 6H, $2CH_3$), 1.50 (t, 3H, J = 7 Hz, CH_3CH_2O), 2.66 (s, 2H, CH_2), 3.86 (s, 3H, CH_3O), 4.13 (q, 2H, J = 7 Hz, CH_3CH_2O), 6.38 (s, 1H, 8-H), 7.28 (s, 1H, 5-H)	250 (M^+, 69), 235 (100)
6e	CH_3	C_2H_5	8	8	86	51-52	1684	1.38 (t, 3H, J = 7 Hz, CH_3CH_2O), 1.50 (s, 6H, $2CH_3$), 2.70 (s, 2H, CH_2), 3.91 (s, 3H, CH_3O), 4.07 (q, 2H, J = 7 Hz, CH_3CH_2O), 6.60 (d, 1H, J = 10 Hz, 6-H), 7.65 (d, 1H, J = 10 Hz, 5-H)	250 (M^+, 100), 235 (88)
6f	C_2H_5	CH_3	8	10	83	oil	1683	1.47 (t, 3H, J = 7 Hz, CH_3CH_2O), 1.51 (s, 6H, $2CH_3$), 2.68 (s, 2H, CH_2), 3.85 (s, 3H, CH_3O), 4.15 (q, 2H, J = 7 Hz, CH_3CH_2O), 6.58 (d, 1H, J = 10 Hz, 6-H), 7.62 (d, 1H, J = 10 Hz, 5-H)	250 (M^+, 52), 235 (100)
6g	CH_3	CH_3	5	60	92	104-105 [b]	1684	1.45 (s, 6H, $2CH_3$), 2.66 (s, 2H, CH_2), 3.81 (s, 3H, CH_3O), 3.89 (s, 3H, CH_3O), 6.04 (m, 2H, ArH)	236 (M^+, 55), 221 (25), 180 (100)
6h	CH_3	CH_3	6	8	94	105-106 [c]	1670	1.47 (s, 6H, $2CH_3$), 2.67 (s, 2H, CH_2), 3.86 (s, 3H, CH_3O), 3.92 (s, 3H, CH_3O), 6.42 (s, 1H, 8-H), 7.27 (s, 1H, 5-H)	236 (M^+, 60), 221 (100)
6i	CH_3	CH_3	8	5	93	75-76 [d]	1690	1.50 (s, 6H, $2CH_3$), 2.67 (s, 2H, CH_2), 3.85 (s, 3H, CH_3O), 3.91 (s, 3H, CH_3O), 6.60 (d, 1H, J = 10 Hz, 6-H), 7.64 (d, 1H, J = 10 Hz, 5-H)	236 (M^+, 78), 221 (90), 181 (100)

[a] Yield of recrystallized compound (from ethanol). [b] Lit mp 104-105° [12]. [c] Lit mp 106° [10,14]. [d] Lit mp 76° [15].

Table 5

Dialkoxy-2,2-dimethyl-2H-chromenes **7a-i** Prepared

No.	R	R^1	Position of OR^1	Reaction time (hour) [a] Reduction	Dehydration	Yield (%) [b]	^1H NMR (deuteriochloroform) δ (ppm)	MS m/e (%)
7a	CH_3	C_2H_5	5	1.5	2	87	1.41 (s, 6H, $2CH_3$ + t, 3H, J = 7 Hz, CH_3CH_2O), 3.75 (s, 3H, CH_3O), 3.97 (q, 2H, J = 7 Hz, CH_3CH_2O), 5.41 (d, 1H, J = 10 Hz, 3-H), 6.01 (m, 2H, ArH), 6.60 (d, 1H, J = 10 Hz, 4-H)	234 (M^+, 40), 219 (100), 191 (29)

7b	C_2H_5	CH_3	5	1	2.5	80	1.38 (t, 3H, J = 7 Hz, CH_3CH$_2$O), 1.42 (s, 6H, 2CH$_3$), 3.77 (s, 3H, CH$_3$O), 3.98 (q, 2H, J = 7 Hz, CH$_3$CH_2O), 5.40 (d, 1H, J = 10 Hz, 3-H), 6.02 (m, 2H, ArH), 6.57 (d, 1H, J = 10 Hz, 4-H)	234 (M$^+$, 45), 219 (100), 191 (28)
7c	CH_3	C_2H_5	6	1.5	1	89	1.43 (s, 6H, 2CH$_3$ + t, 3H, J = 7 Hz, CH_3CH$_2$O), 3.83 (s, 3H, CH$_3$O), 4.01 (q, 2H, J = 7 Hz, CH$_3$CH_2O), 5.46 (d, 1H, J = 10 Hz, 3-H), 6.22 (d, 1H, J = 10 Hz, 4-H), 6.42 (s, 1H, ArH), 6.55 (s, 1H, ArH)	234 (M$^+$, 54), 219 (100), 191 (47)
7d	C_2H_5	CH_3	6	2	1.5	85 [c]	1.42 (s, 6H, 2CH$_3$), 1.48 (t, 3H, J = 7 Hz, CH_3CH$_2$O), 3.80 (s, 3H, CH$_3$O), 4.05 (q, 2H, J = 7 Hz, CH$_3$CH_2O), 5.45 (d, 1H, J = 10 Hz, 3-H), 6.22 (d, 1H, J = 10 Hz, 4-H), 6.40 (s, 1H, ArH), 6.53 (s, 1H, ArH)	234 (M$^+$, 77), 219 (100), 191 (80)
7e	CH_3	C_2H_5	8	1	2	82	1.37 (t, 3H, J = 7 Hz, CH_3CH$_2$O), 1.47 (s, 6H, 2CH$_3$), 3.83 (s, 3H, CH$_3$O), 4.12 (q, 2H, J = 7 Hz, CH$_3$CH_2O), 5.50 (d, 1H, J = 10 Hz, 3-H), 6.26 (d, 1H, J = 10 Hz, 4-H), 6.40 (d, 1H, J = 8 Hz, ArH), 6.66 (d, 1H, J = 8 Hz, ArH)	234 (M$^+$, 29), 219 (100), 191 (18)
7f	C_2H_5	CH_3	8	1.5	2.5	84	1.45 (s, 6H, 2CH$_3$ + t, 3H, J = 7 Hz, CH_3CH$_2$O), 3.87 (s, 3H, CH$_3$O), 4.07 (q, 2H, J = 7 Hz, CH$_3$CH_2O), 5.50 (d, 1H, J = 10 Hz, 3-H), 6.25 (d, 1H, J = 10 Hz, 4-H), 6.40 (d, 1H, J = 8 Hz, ArH), 6.65 (d, 1H, J = 8 Hz, ArH)	234 (M$^+$, 31), 219 (100), 191 (25)
7g	CH_3	CH_3	5	2	2	90	1.42 (s, 6H, 2CH$_3$), 3.75 (s, 3H, CH$_3$O), 3.80 (s, 3H, CH$_3$O), 5.40 (d, 1H, J = 10 Hz, 3-H), 6.02 (m, 2H, ArH), 6.57 (d, 1H, J = 10 Hz, 4-H)	220 (M$^+$, 35), 205 (100),
7h	CH_3	CH_3	6	1.5	1	89 [d]	1.42 (s, 6H, 2CH$_3$), 3.80 (s, 3H, CH$_3$O), 3.85 (s, 3H, CH$_3$O), 5.41 (d, 1H, J = 10 Hz, 3-H), 6.26 (d, 1H, J = 10 Hz, 4-H), 6.42 (s, 1H, ArH), 6.57 (s, 1H, ArH)	220 (M$^+$, 48), 205 (100)
7i	CH_3	CH_3	8	1	1.5	92	1.47 (s, 6H, 2CH$_3$), 3.80 (s, 3H, CH$_3$O), 3.84 (s, 3H, CH$_3$O), 5.51 (d, 1H, J = 10 Hz, 3-H), 6.24 (d, 1H, J = 10 Hz, 4-H), 6.42 (d, 1H, J = 8 Hz, ArH), 6.67 (d, 1H, J = 8 Hz, ArH)	220 (M$^+$, 38), 205 (100)

[a] Averaged times based on tlc monitoring of the reaction. [b] Yield based on the amount of **6a-i**. [c] Precocene 3 [7]. [d] Precocene 2 (mp 45-46°, reported mp 46-47° [21]).

Typical Procedure.

Compound **3b** (104 g, 0.5 mole) was dissolved in 5% aqueous sodium hydroxide solution (1800 ml) and stirred at 25° for 1 hour. The solution was cooled to below 10° and acidified to *p*H 1 with concentrated hydrochloric acid. The solid was filtered, washed with water and dried. The crude product was recrystallized from ethanol/water, 95.7 g (92%), mp 208-209°. Other data are given in Table 2.

7,8-Dihydroxy-2,2-dimethyl-4-chromanone (**4c**).

Typical Procedure.

Pyrogallol (**1c**, 126.1 g, 1 mole), 3-methylbut-2-enoic acid (**2**, 100.2 g, 1 mole), zinc chloride (unfused, 200 g, 1.39 moles) and phosphoryl chloride (1352 g, 800 ml, 8.81 moles) were mixed and stirred at 50° for 5 hours. The reaction mixture was worked up as described above. The crude product **4c** was crystallized from ethanol/water to give prisms, 166.5 g (80%), mp 142-143°. Other data are given in Table 2.

7-*O*-Alkylated-monohydroxy-2,2-dimethyl-4-chromanones **5a-f**.

General Procedure.

The starting dihydroxy-2,2-dimethyl-4-chromanones **4a-c** (20.8 g, 0.1 mole) were dissolved in *N,N*-dimethylformamide (100 ml) and stirred with potassium carbonate (16.5 g, 0.12 mole) (and potassium iodide (0.5 g) in those cases when the alkyl halide was not an iodide) and methyl iodide or ethyl bromide (0.11-0.14 mole, depending on the boiling point and reactivity) at 80°. (Reaction times and other data are listed in Table 3). When the reaction was completed, the inorganic solid was filtered and the solvent was removed under vacuum. A 5% solution of sodium hydroxide (150 ml) was added and the mixture was extracted twice with dichloromethane (100-100 ml). The alkaline aqueous solution was acidified with concentrated hydrochloric acid to *p*H 1 (at or below 10°) and the precipitate formed **5** was filtered, washed with water, dried and recrystallized from ethanol or ethanol/water.

Table 6

Carbon Chemical Shifts for Compounds **7a-i** (in deuteriochloroform)

Compound	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	C-9, C-10	OCH_3	OCH_2CH_3	OCH_2CH_3
7a	76.18	125.79	117.00	104.10	161.13	92.53	155.64	94.23	154.47	27.86	55.31	63.95	14.76
7b	76.05	125.69	116.70	104.00	160.30	91.92	156.10	94.53	154.60	27.69	55.41	63.39	14.70
7c	75.85	128.08	122.04	113.23	112.62	150.58	147.65	101.38	142.34	27.73	55.86	65.48	15.01
7d	75.77	128.08	122.09	113.22	110.77	149.32	147.44	102.46	143.56	27.69	56.74	64.28	14.77
7e	76.17	128.29	122.09	116.17	120.49	105.64	153.90	138.10	146.68	27.88	56.01	64.53	14.83
7f	76.21	128.37	122.21	116.26	120.75	105.67	152.94	138.20	146.59	27.88	60.59	64.50	14.94
7g	76.05	125.73	116.66	104.17	161.00	91.38	156.10	94.05	154.65	27.70	55.39	–	–
											55.16		
7h	75.94	128.19	121.94	113.12	110.09	149.84	147.35	101.18	143.20	27.67	56.64	–	–
											55.90		
7i	76.29	128.44	122.16	116.33	120.80	104.16	153.60	137.76	146.49	27.89	60.70	–	–
											55.96		

Table 7

Microanalysis Data of Precocenes **7a-i** and Intermediates **3-6**

No.	Molecular formula	*Anal.*/Calcd. C(%)	H(%)	*Anal.*/Found C(%)	H(%)
3b	$C_{11}H_{12}O_4$	63.45	5.81	63.74	5.90
3c	$C_{11}H_{12}O_4$	63.45	5.81	63.70	5.71
4a	$C_{11}H_{12}O_4$	63.45	5.81	63.58	5.88
4b	$C_{11}H_{12}O_4$	63.45	5.81	63.67	5.74
4c	$C_{11}H_{12}O_4$	63.45	5.81	63.80	5.82
5a	$C_{12}H_{14}O_4$	64.85	6.30	64.97	6.38
5b	$C_{13}H_{16}O_4$	66.08	6.83	66.30	6.90
5c	$C_{12}H_{14}O_4$	64.85	6.30	64.55	6.20
5d	$C_{13}H_{16}O_4$	66.08	6.83	66.12	6.88
5e	$C_{12}H_{14}O_4$	64.85	6.30	64.70	6.26
5f	$C_{13}H_{16}O_4$	66.08	6.83	66.20	6.92
6a	$C_{14}H_{18}O_4$	67.18	7.25	67.26	7.22
6b	$C_{14}H_{18}O_4$	67.18	7.25	67.30	7.30
6c	$C_{14}H_{18}O_4$	67.18	7.25	67.02	7.32
6d	$C_{14}H_{18}O_4$	67.18	7.25	67.40	7.20
6e	$C_{14}H_{18}O_4$	67.18	7.25	67.35	7.31
6f	$C_{14}H_{18}O_4$	67.18	7.25	67.20	7.26
6g	$C_{13}H_{16}O_4$	66.08	6.83	66.22	6.90
6h	$C_{13}H_{16}O_4$	66.08	6.83	66.30	6.87
6i	$C_{13}H_{16}O_4$	66.08	6.83	66.09	6.80
7a	$C_{14}H_{18}O_3$	71.77	7.74	71.87	7.80
7b	$C_{14}H_{18}O_3$	71.77	7.74	71.90	7.83
7c	$C_{14}H_{18}O_3$	71.77	7.74	71.94	7.70
7d	$C_{14}H_{18}O_3$	71.77	7.74	71.70	7.69
7e	$C_{14}H_{18}O_3$	71.77	7.74	71.80	7.72
7f	$C_{14}H_{18}O_3$	71.77	7.74	71.97	7.78
7g	$C_{13}H_{16}O_3$	70.85	7.32	70.90	7.33
7h	$C_{13}H_{16}O_3$	70.85	7.32	70.96	7.40
7i	$C_{13}H_{16}O_3$	70.85	7.32	70.87	7.30

2,2-Dimethyldialkoxychromanones **6a-f**.

General Procedure.

Monohydroxychromanones **5a-f** (0.1 mole) were dissolved in *N,N*-dimethylformamide (100 ml) and stirred with potassium carbonate (27.6 g, 0.2 mole) (and potassium iodide in those cases when the alkyl halide was not an iodide) and methyl iodide or ethyl bromide (0.2-0.3 mole) at 80°. (Reaction times and other data are listed in Table 4). The mixture was then poured onto crushed ice (300 g), the precipitate was filtered, washed with water, dried and recrystallized from ethanol. When the product was separated as an oil, then the mixture was extracted with dichloromethane (3 x 100 ml). The combined dichloromethane layer was washed with 3% aqueous sodium hydroxide solution (2 x 100 ml), water (2 x 100), brine (2 x 100 ml) and dried with magnesium sulfate. The solvent was removed under reduced pressure and the residue thus obtained was crystallized from ethanol.

2,2-Dimethyldimethoxychromanones **6g-i**.

General Procedure.

Dihydroxy-2,2-dimethyl-4-chromanones **4a-c** (0.1 mole) were dissolved

in *N,N*-dimethylformamide (150 ml) and stirred with potassium carbonate (41.4 g, 0.3 mole) and methyl iodide (0.3-0.5 mole) at 80°. The reaction mixture was poured onto crushed ice (300 g), filtered, the precipitate washed with water and recrystallized. Reaction times, yields and other data are in Table 4.

Dialkoxy-2,2-dimethyl-2*H*-chromenes **7a-i** Including Precocene 2 (**7h**) and Precocene 3 (**7d**).

General Procedure.

The corresponding dialkoxy-2,2-dimethyl-4-chromanone **6a-i** (0.1 mole) was dissolved in methanol (200 ml) and stirred at 25° for the time given in Table 5. During this time sodium borohydride (10 g, 0.26 mole) was added in portions to the reaction mixture. The solvent was removed in vacuum and water (200 ml) was added to the residue. This mixture was extracted with dichloromethane (3 x 100 ml). The extract was washed with water (3 x 100 ml), dried with sodium sulfate and the solvent evaporated. The residue was then dissolved in tetrahydrofuran (150 ml) and treated with 4*M* hydrochloric acid (200 ml) at (or below) 25°. (Reaction times for the individual chromenes are listed in Table 5). The reaction mixture was subsequently extracted with ether (3 x 100 ml), and the combined ether layers were washed with 2% aqueous sodium hydroxide solution (2 x 100 ml), water (3 x 100 ml), and brine (2 x 100 ml), and dried with sodium sulfate. The solvent was evaporated in vacuum. Yields of **7a-i** (based on **6a-i**) and other data are given in Table 5. Analytical samples were obtained by column chromatography (Silica gel, hexane/ether = 9/1).

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