NOVEL AND SELECTIVE SYNTHESES OF NEW ANALOGUES OF PRECOCENE-2 AND PRECOCENE-3 CONTAINING 5-METHYL- OR 8-METHYL-SUBSTITUENTS[1]

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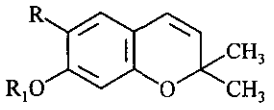
Abstract — New analogues of precocene-2 and precocene-3 containing 5-methyl- or 8-methyl-substituents have been synthesised in good yields utilising regioselective *O*-alkylation of 6,7-dihydroxy-2,2,5-trimethyl-4-chromanone and 6,7-dihydroxy-2,2,8-trimethyl-4-chromanone as the key step.

Precocenes (**1**) are well known proallatocidins[2] and nematotoxic agents[3] isolated from *Ageratum houstonianum*.[4] They cause premature metamorphosis and other symptoms of juvenile hormone deficiency on sensitive insect species.[5] The attractive bioactivity of these compounds stimulated an extensive chemical and biological investigations to elucidate their mode of action and structure-activity relationships.[6]



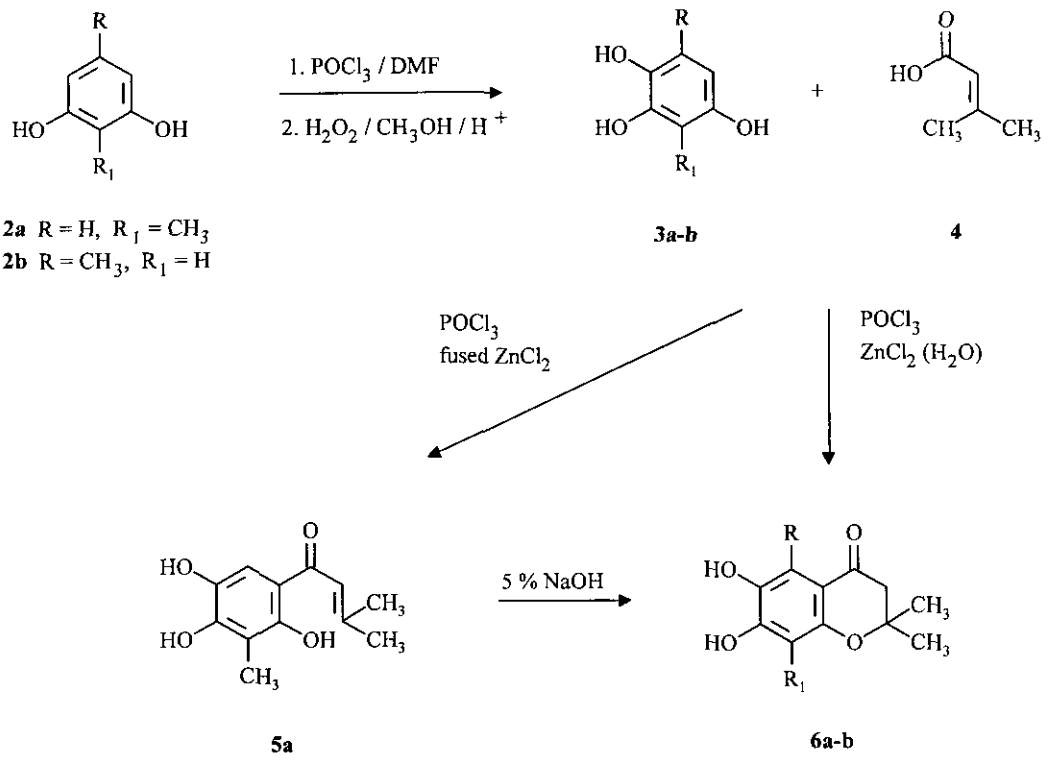
	R	R_1	
1a	H	CH_3	Precocene-1
1b	CH_3O	CH_3	Precocene-2
1c	CH_3O	C_2H_5	Precocene-3

Results on mode of action studies have provided strong evidence that precocenes undergo an oxidative biotransformation into highly reactive 3,4-epoxides by microsomal cytochrome P-450 dependent monooxygenases, within the *corpora allata*, the glands where the juvenile hormones (JHs) are biosynthesised. These epoxides would cause necrosis of the gland with the ensuing suppression of JH biosynthesis.[7] Structure-activity relationship investigations have shown that the presence of C-6 and C-7 alkoxy substituents is a fundamental requirement to elicit the precocious activity of these 2,2-dimethyl-2*H*-chromene derivatives. It is also well documented that the precocene-2 (**1b**) has more pronounced precocious activity than precocene-1 (**1a**).[8] The 7-ethoxy-6-methoxy-2,2-dimethyl-2*H*-chromene (precocene-3, **1c**) was found to be the most active synthetic precocene analogue.[9] There is also a report on the activity-enhancing effect exerted by the C-5 methyl substituent in the series of precocene-1 (**1a**) analogues.[10] Although numerous precocene derivatives have been synthesised in different laboratories,[11] a careful literature search revealed that the synthesis of such 2,2-dimethyl-2*H*-chromene systems, combining these seemingly important structural features, had not been reported heretofore. Consequently, we decided to synthesise 5-methyl- and 8-methyl-6,7-dialkoxy-2,2-dimethyl-2*H*-chromenes (**10**) from common 4-chromanone intermediates **6a,b** (see Scheme 1) in order to assess the effect of these substituent combinations on the precocious activity.

Thus, 2-methylresorcinol (**2a**) and orcinol (**2b**) were formylated under Vilsmeier conditions and subsequently converted[12] by H_2O_2 in acidic MeOH to the corresponding methyl-trihydroxybenzenes (**3a,b**) in 68 and 72% yields, respectively. Conversion to the 4-chromanones (**6a-b**) was accomplished by reaction of **3a,b** with 3-methylbut-2-enoic acid (**4**) in $POCl_3$ in the presence of $ZnCl_2$.[13] Applying the original procedure to **3a**,[13] the use of fused $ZnCl_2$ made possible the isolation of the open-chain intermediate (**5a**) in good yield (80%). Tlc monitoring of this reaction showed that the formation of **5a** was completed within 3 hours. However its cyclization to **6a** took place very slowly (about 40 hours) in this system together with the formation of undesired side products. It is worth noting that **5a** can be cyclised easily in 5% NaOH solution to the corresponding 4-chromanone (**6a**) in 95% yield.

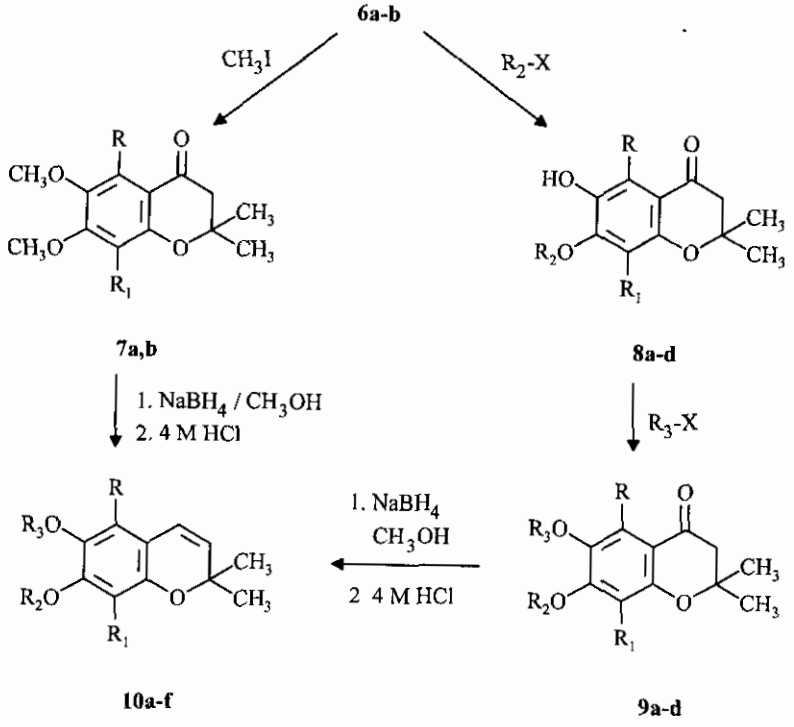
In the case of the reaction of 1-methyl-2,3,5-trihydroxybenzene (**3b**), however, we did not find the corresponding intermediate. Tlc and ^1H nmr monitoring of this reaction revealed that the reaction mixture contains **6b** from the beginning of the reaction. This is in agreement with earlier observations.[14,15] The use of commercial $ZnCl_2$ (containing 5-6% H_2O) resulted in 10-fold decrease in reaction times. By this modified method[15] both 4-chromanones (**6a,b**) were obtained directly in 80-85% yields.

Scheme 1



These dihydroxy-4-chromanones appeared to be useful intermediates for regioselective *O*-alkylations[11,16] to obtain analogues of precocene-3 precursor dialkoxy-4-chromanones (**9a-d**) (Scheme 2). Accordingly, regioselective *O*-alkylation of **6a,b** with either methyl or ethyl halides resulted in the formation of the corresponding 7-*O*-alkylated-6-hydroxy-4-chromanones (**8a-d**). These compounds were isolated in 82-90% yields, then were *O*-alkylated again with ethyl or methyl halides, furnishing the 5-methyl- and 8-methyl-6,7-dialkoxy-2,2-dimethyl-4-chromanones (**9a-d**) in 83-93% yields. The efficient synthesis of these 4-chromanones followed by reduction and dehydration led to analogues of precocene-3, **10d,f** and their regioisomers (**10c,e**) containing 5-methyl- and 8-methyl-substituents. The corresponding precocene-2 analogues were also prepared *via* the route **6a,b** → **7a,b** → **10a,b** in 68 and 78% overall yields, respectively (see Tables 1, 2).

Scheme 2



	R	R_1	R_2	R_3
8a	H	CH_3	CH_3	—
8b	H	CH_3	CH_3CH_2	—
8c	CH_3	H	CH_3	—
8d	CH_3	H	CH_3CH_2	—
9a	H	CH_3	CH_3	CH_3CH_2
9b	H	CH_3	CH_3CH_2	CH_3
9c	CH_3	H	CH_3	CH_3CH_2
9d	CH_3	H	CH_3CH_2	CH_3
10a	H	CH_3	CH_3	CH_3
10b	CH_3	H	CH_3	CH_3
10c	H	CH_3	CH_3	CH_3CH_2
10d	H	CH_3	CH_3CH_2	CH_3
10e	CH_3	H	CH_3	CH_3CH_2
10f	CH_3	H	CH_3CH_2	CH_3

Table 1 Physical and Spectral Data of Compounds (**5-10**) Prepared

Product[a]	Method	Yield[b] (%)	mp (°C)	^{1}H-Nmr ($CDCl_3$/TMS) δ, *J* (Hz)	Ms (70 eV) *m/z* (%)
5a	A	80	137-140	1.98 (d, *J* = 1.5, 3H), 2.10 (s, 3H), 2.18 (d, *J* = 1.5, 3H), 6.20 (br s, 2H), 6.60 (m, 1H), 7.10 (s, 1H), 13.60 (s, 1H)	222 (M^+, 11), 207 (100), 167 (27), 166 (9), 83 (34)
6a	B	95	189-192	1.47 (s, 6H), 2.12 (s, 3H), 2.65 (s, 2H), 6.50 (br s, 2H), 7.37 (s, 1H)	222 (M^+, 47), 207 (100), 167 (80), 166 (58), 138 (43)
6b	C	85	217-218[c]	1.33 (s, 6H), 2.45 (s, 3H), 2.62 (s, 2H), 6.18 (s, 1H), 8.00 (br s, 1H), 10.50 (s, H)	222 (M^+, 58), 207 (61), 167 (61), 166 (100), 83 (80)
7a	D	87	58-60	1.48 (s, 6H), 2.10 (s, 3H), 2.70 (s, 2H), 3.82 (s, 3H), 3.86 (s, 3H), 7.24 (s, 1H)	250 (M^+, 64), 235 (100), 219 (10), 195 (87), 179 (15)
7b	D	91	125-127	1.45 (s, 6H), 2.58 (s, 3H), 2.67 (s, 2H), 3.72 (s, 3H), 3.90 (s, 3H), 6.30 (s, 1H)	250 (M^+, 64), 235 (42), 194 (100), 179 (85), 151 (30)
8a	E	82	138-140	1.45 (s, 6H), 2.15 (s, 3H), 2.65 (s, 2H), 3.80 (s, 3H), 5.40 (br s, 1H), 7.20 (s, 1H)	236 (M^+, 50), 221 (100), 181 (80) , 152 (38), 137 (13)
8b	E	89	124-126	1.45 (s + t, *J* = 7, 6H +3H), 2.18 (s, 3H), 2.70 (s, 2H), 4.01 (q, *J* = 7, 2H), 5.50 (br s, 1H), 7.25 (s, 1H)	250 (M^+, 65), 235 (100), 195 (55), 167 (60), 150 48)
8c	E	90	108-110	1.45 (s, 6H), 2.61 (s, 3H), 2.68 (s, 2H), 3.92 (s, 3H), 5.32 (br s, 1H), 6.30 (s, 1H)	236 (M^+, 50), 221 (42), 180 (100) , 137 (19)
8d	E	87	170-172	1.45 (s, 6H), 1.50 (t, *J* = 7, 3H), 2.58 (s, 3H), 2.66 (s, 2H), 4.14 (q, *J* = 7, 2H), 5.37 (br s, 1H), 6.27 (s, 1H)	250 (M^+, 48), 235 (33), 194 (100), 166 (32), 137 (10)
9a	F	86	76-78	1.45 (s + t, *J* = 7, 6H +3H), 2.10 (s, 3H), 2.65 (s, 2H), 3.90 (s, 3H), 4.08 (q, *J* = 7, 2H), 7.20 (s, 1H)	264 (M^+, 70), 249 (100), 209 (80), 179 (45), 151 (20)
9b	F	83	oil	1.38 (t, *J* = 7, 3H), 1.45 (s, 6H), 2.10 (s, 3H), 2.66 (s, 2H), 3.81 (s, 3H), 4.10 (q, *J* = 7, 2H), 7.23 (s, 1H)	264 (M^+, 75), 249 (100), 209 (60), 181 (62), 163 (40)
9c	F	89	73-74	1.37 (t, *J* = 7, 3H), 1.45 (s, 6H), 2.57 (s, 3H), 2.66 (s, 2H), 3.87 (s, 3H), 3.90 (q, *J* = 7, 2H), 6.30 (s, 1H)	264 (M^+, 46), 249 (18), 235 (12), 179 (100), 151 (20)
9d	F	93	105-107	1.44 (s, 6H), 1.48 (t, *J* = 7, 3H), 2.58 (s, 3H), 2.68 (s, 2H), 3.72 (s, 3H), 4.08 (q, *J* = 7, 2H), 6.28 (s, 1H)	264 (M^+, 65), 249 (40), 208 (100), 193 (56), 165 (20)

Table 1 continued

10a	G	79	oil	1.43 (s, 6H), 2.09 (s, 3H), 3.76 (s, 3H), 3.80 (s, 3H), 5.53 (d, J = 10, 1H), 6.70 (d, J = 10, 1H), 6.92 (s, 1H)	234 (M^+, 82), 219 (100), 203 (25), 175 (24)
10b	G	86	oil	1.42 (s, 6H), 2.20 (s, 3H), 3.70 (s, 3H), 3.80 (s, 3H), 5.52 (d, J = 10, 1H), 6.30 (s, 1H), 6.45 (d, J = 10, 1H)	234 (M^+, 41), 219 (100), 203 (10), 175 (14)
10c	G	78	oil	1.40 (s + t, J = 7, 6H +3H), 2.09 (s, 3H), 3.80 (s, 3H), 4.00 (q, J = 7, 2H), 5.53 (d, J = 10, 1H), 6.22 (d, J = 10, 1H), 6.43 (s, 1H)	248 (M^+, 28), 233 (100), 205 (20), 190 (11)
10d	G	87	oil	1.35 (t, J = 7, 3H), 1.43 (s, 6H), 2.10 (s, 3H), 3.75 (s, 3H), 3.95 (q, J = 7, 2H), 5.53 (d, J = 10, 1H), 6.22 (d, J = 10, 1H), 6.44 (s, 1H)	248 (M^+, 25), 233 (100), 205 (80), 190 (15)
10e	G	83	oil	1.37 (t, J = 7, 3H), 1.42 (s, 6H), 2.21 (s, 3H), 3.80 (s, 3H), 3.91 (q, J = 7, 2H), 5.52 (d, J = 10, 1H), 6.30 (s, 1H), 6.45 (d, J = 10, 1H)	248 (M^+, 70), 233 (100), 219 (29), 205 (80), 175 (26), 145 (31)
10f	G	85	oil	1.40 (s, 6H), 1.47 (t, J = 7, 3H), 2.22 (s, 3H), 3.75 (s, 3H), 4.02 (q, J = 7, 2H), 5.51 (d, J = 10, 1H), 6.27 (s, 1H), 6.44 (d, J = 10, 1H)	248 (M^+, 61), 233 (100), 205 (82), 190 (42), 145 (11)

[a] Satisfactory microanalyses obtained: C ± 0.35, H ± 0.25.

[b] Based on isolated products.

[c] Lit.,[19] mp 216-217 °C.

Bioactivity studies of novel precocene derivatives (**10a-f**) have been performed on larvae *Oncopeltus fasciatus, Pieris brassicae* and *Locusta migratoria*.[10,17] Results of these investigations have shown that the analogues had strong precocious activity on larvae *Oncopeltus fasciatus* but failed to show any antiallatal activity on *Locusta migratoria*. The studies also provided clear-cut evidence that both 5-methyl- and 8-methyl-substituents could considerably influence the caste (insect species) specificity as well as the bioactivity of these novel synthetic precocenes on different larval-stages.[18]

In conclusion, we have elaborated novel and selective syntheses of new analogues of natural and synthetic precocenes (**10**) from common 4-chromanone intermediates (**6**). Our synthetic route seems to be generally applicable for the synthesis of further synthetic precocenes containing different alkoxy substituens at C-6 and C-7 positions.

Table 2 Microanalyses of compounds (**5-10**)

Compound	Molecular formula	Molecular weight	Calculated / Found	
			C	H
5a	$C_{12}H_{14}O_4$	222.24	63.14 / 63.00	6.81 / 6.93
6a	$C_{12}H_{14}O_4$	222.24	63.14 / 63.29	6.81 / 6.74
6b	$C_{12}H_{14}O_4$	222.24	63.14 / 63.05	6.81 / 6.89
7a	$C_{14}H_{18}O_4$	250.29	67.18 / 67.39	7.25 / 7.38
7b	$C_{14}H_{18}O_4$	250.29	67.18 / 67.50	7.25 / 7.44
8a	$C_{13}H_{16}O_4$	236.27	66.08 / 66.37	6.83 / 6.98
8b	$C_{14}H_{18}O_4$	250.29	67.18 / 67.42	7.25 / 7.40
8c	$C_{13}H_{16}O_4$	236.27	66.08 / 65.94	6.83 / 6.78
8d	$C_{14}H_{18}O_4$	250.29	67.18 / 67.39	7.25 / 7.48
9a	$C_{15}H_{20}O_4$	264.32	68.16 / 68.01	7.63 / 7.88
9b	$C_{15}H_{20}O_4$	264.32	68.16 / 68.42	7.63 / 7.52
9c	$C_{15}H_{20}O_4$	264.32	68.16 / 68.39	7.63 / 7.85
9d	$C_{15}H_{20}O_4$	264.32	68.16 / 67.96	7.63 / 7.82
10a	$C_{14}H_{18}O_3$	234.29	71.77 / 71.94	7.74 / 7.89
10b	$C_{14}H_{18}O_3$	234.29	71.77 / 71.85	7.74 / 7.98
10c	$C_{15}H_{20}O_3$	248.32	72.55 / 72.76	8.12 / 8.29
10d	$C_{15}H_{20}O_3$	248.32	72.55 / 72.38	8.12 / 8.33
10e	$C_{15}H_{20}O_3$	248.32	72.55 / 72.90	8.12 / 8.34
10f	$C_{15}H_{20}O_3$	248.32	72.55 / 72.28	8.12 / 8.01

EXPERIMENTAL

Melting points were determined with a Koffler hot-stage apparatus and are uncorrected. Analytical thin-layer chromatography was performed on precoated aluminium-backed 0.2 mm silica gel plates. Column chromatography was carried out with Kieselgel 60 silica gel using 4:1 hexane-Et_2O as the eluent. ^1H Nmr spectra were determined for solutions in deuteriochloroform with TMS internal reference on a Varian Gemini-200 instrument. Ms data were obtained on a VG TRIO-2 spectrometer in EI mode at 70 eV. Microanalyses were performed by Microlaboratory, L. Kossuth University, Debrecen, Hungary. Solvents were used either as purchased or dried and purified by standard methods.

Preparation of Starting Materials (3). Methyl-trihydroxybenzenes (**3a,b**) were prepared from the corresponding methylresorcinols (**2a,b**) according to known procedures[12,19]: **1-Methyl-2,3,6-trihydroxybenzene** (**3a**) Yield: 68%; mp 118-120 °C (from benzene), (lit.,[20] mp 121.5 °C, from benzene); **1-Methyl-2,3,5-trihydroxybenzene** (**3b**) Yield: 72%; mp 146-147 °C (from benzene), (lit.,[19] mp 147-149 °C, from benzene).

1-(3'-Methyl-2',4',5'-trihydroxyphenyl)-3-methyl-1-oxo-2-butene (5a):

Method A: To a stirred mixture of $POCl_3$ (80 ml, 881 mmol) and 3-methylbut-2-enoic acid (10.02 g, 100 mmol), fused $ZnCl_2$ (20 g, 147 mmol) and 1-methyl-2,3,6-trihydroxybenzene (14.01 g, 100 mmol) were added. The mixture was stirred at 25 °C for 3 h, and then poured onto crushed ice (500 g). The separated solid was filtered, washed with H_2O and dried. The crude product thus obtained was sufficiently pure for use in the following reaction step. It can be purified by recrystallisation from EtOH/H_2O to afford **5a** (Tables 1, 2).

6,7-Dihydroxy-2,2,8-trimethyl-4-chromanone (6a):

Method B: Compound (**5a**) (11.10 g, 50 mmol) was dissolved in 5 % aqueous NaOH solution (180 ml) and stirred at room temperature for 1 h. The solution was cooled below 10 °C and acidified to pH 1 with concentrated HCl. The solid was filtered, washed with H_2O and dried. The crude product was recrystallised from EtOH/H_2O to afford **6a** (Tables 1, 2).

6,7-Dihydroxy-2,2,5-trimethyl-4-chromanone (6b):

Method C: 1-Methyl-2,3,5-trihydroxybenzene (14.01 g, 100 mmol), 3-methylbut-2-enoic acid (10.02 g, 100 mmol), $ZnCl_2$ (unfused, 20 g, 139 mmol) and $POCl_3$ (80 ml, 881 mmol) were mixed and stirred at 50 °C for 4 h. The reaction mixture was worked up as described above. The crude product was crystallised from EtOH/H_2O to afford **6b** (Tables 1, 2).

6,7-Dimethoxy-trimethyl-4-chromanones 7a,b; General procedure:

Method D: Dihydroxy-trimethyl-4-chromanones (**6a,b**) (100 mmol) were dissolved in DMF (150 ml) and stirred with K_2CO_3 (41.4 g, 300 mmol) and MeI (42.6-70.9 g, 300-500 mmol) at 80 °C. When starting materials were consumed (monitored by tlc) the reaction mixture was poured onto crushed ice (300 g), then the mixture was extracted with CH_2Cl_2 (3x100 ml). The combined CH_2Cl_2 layer was washed with 3% aqueous NaOH solution (2x100 ml), H_2O (2x100 ml) and brine (2x100 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue thus obtained was crystallised from EtOH to afford compounds (**7a,b**) (Tables 1, 2).

7-Alkoxy-6-hydroxy-trimethyl-4-chromanones 8a-d; General procedure:

Method E: The starting dihydroxy-trimethyl-4-chromanones (**6a,b**) (100 mmol) were dissolved in DMF (150 ml) and stirred with K_2CO_3 (16.5 g, 120 mmol) and sometimes KI (0.5 g added for EtBr). MeI or EtBr (110-140 mmol, depending on the boiling point and reactivity) were added and the reaction mixture was heated at 80 °C. When the reaction was complete (tlc monitoring), the inorganic solid was filtered and the solvent was removed under vacuum. A 5% solution of NaOH (150 ml) was added and the mixture was extracted with CH_2Cl_2 (2x100 ml). The alkaline aqueous solution was acidified with concentrated HCl to pH 1 (at or below 10 °C) and the precipitate which formed was filtered, washed with H_2O, dried and recrystallised from EtOH or EtOH/H_2O to afford compounds (**8a-d**) (Tables 1, 2).

6,7-Dialkoxy-trimethyl-4-chromanones 9a-d; General procedure:

Method F: 6-Hydroxy-7-alkoxy-trimethyl-4-chromanones (**8a-d**) (100 mmol) were dissolved in DMF (150 ml) and stirred with K_2CO_3 (27.6 g, 200 mmol) and sometimes KI (0.5 g added for EtBr). MeI or EtBr (200-300 mmol, depending on the boiling point and reactivity) were added and the reaction mixture was heated at 80 °C. When the reaction was complete (tlc monitoring), the reaction mixture was poured onto crushed ice (300 g) and extracted with CH_2Cl_2 (2x100 ml). The combined CH_2Cl_2 layer was washed with 3% aqueous NaOH solution (2x100 ml), H_2O (2x100 ml) and brine (2x100 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue thus obtained was crystallised from EtOH to afford compounds (**9a-d**) (Tables 1, 2).

6,7-Dialkoxy-trimethyl-2*H*-chromenes 10a-f; General Procedure:

Method G: The corresponding 6,7-dialkoxy-trimethyl-4-chromanone (**7a,b**) and (**9a-d**) (10 mmol) was dissolved in MeOH (25 ml) and stirred at 30 °C until all the starting compound was consumed (tlc monitoring). During this period $NaBH_4$ (1 g, 26 mmol) was added in portions to the reaction mixture. The solvent was removed under reduced pressure, and H_2O (20 ml) was added to the residue. This mixture was extracted with CH_2Cl_2 (3x10 ml). The extract was washed with H_2O (3x10 ml) and the solvent evaporated. The residue was then dissolved in THF (15 ml) and treated with 4M HCl (20 ml) below 25 °C. When dehydration was complete (tlc) the reaction mixture was subsequently extracted with Et_2O (3x10 ml) and the combined Et_2O layers were *washed with 2% aqueous* NaOH *solution* (2x10 ml), H_2O (3x10 ml) and brine (2x10 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography to afford compounds (**10a-f**) (Tables 1, 2).

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