

SELECTIVE SYNTHESSES OF ANALOGUES OF THE NATURAL PRECOCENES.
 SYNTHESIS AND REGIOSELECTIVE O-ALKYLATION OF 6-CHLORO- AND
 6-TERT-BUTYL-7,8-DIHYDROXY-2,2-DIMETHYL-4-CHROMANONES

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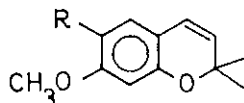
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Abstract - The synthesis of novel benzopyran compounds 16 a-f, analogues of the natural precocenes (1 and 2) is described. These derivatives are obtained via novel synthesis and regioselective O-alkylation of 6-chloro- and 6-tert-butyl-7,8-dihydroxy-2,2-dimethyl-4-chromanones (7 and 12).

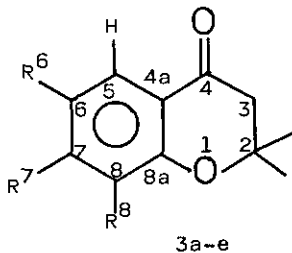
Precocenes (1 and 2) are known inhibitors of juvenile hormone biosynthesis in susceptible insects¹⁻³. These compounds are of natural origin, isolated from Ageratum houstonianum⁴ and other plants^{5,6}. In our earlier reports^{7,8} we described the synthesis of various analogues of the natural precocenes. We introduced novel substituents to the aromatic ring and studied the QSAR⁹ in the case of these new synthetic precocene analogues. Our test media were the migratory locust Locusta migratoria¹⁰ and the nematode Caenorhabditis remanei^{11,12}.



1 R = H Precocene 1

2 R = CH₃O Precocene 2

On the basis of our earlier results¹³, we required 6-chloro- and 6-*tert*-butyl-7,8-dialkoxy-2,2-dimethyl-2H-chromenes (16 a-f). In this paper we describe high-yield syntheses of these novel precocene analogues from common intermediates of 3-type.



Thus, 4-chloropyrogallol (5) was synthesized by the method of Horner and Göwecke¹⁴ (Scheme 1) and treated with 3-methylbut-2-enoic acid (6) in phosphorus oxychloride in the presence of zinc chloride. The chromanone derivative (7) was obtained in 72 % yield. This compound was then monoalkylated in a regioselective manner giving the 8-alkylated derivatives (9 a-d). The corresponding 7,8-dialkoxy derivatives (8 a-e) were also obtained from the reaction mixture. The regioselective synthesis of the 7-monohydroxy compounds (9 a-d) made it possible to introduce a second alkyl group giving (10 a-c) (Scheme 1). Yields, physical and spectral data are summarized in Table 1.

Scheme 1

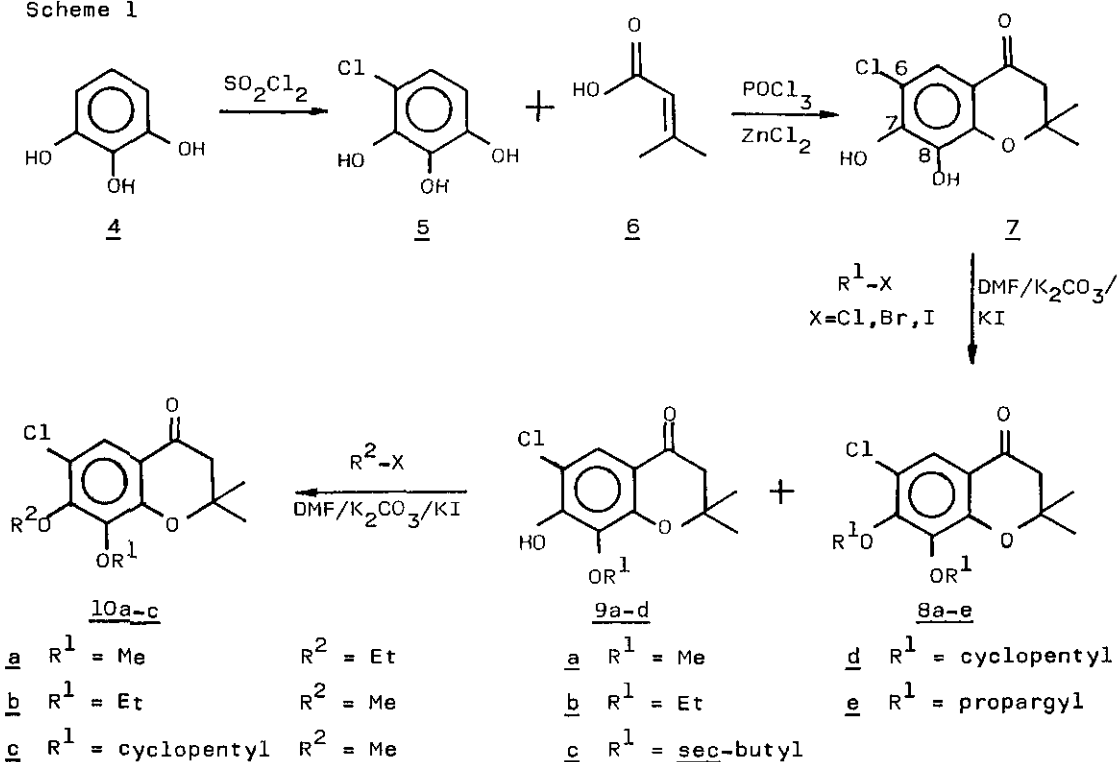


Table 1

Compound	Substituent on		Reaction time ^c (h)	Yield (%)	mp (°C)	¹ H nmr (COCl ₂) (ppm)	EIMS ^d (rel.int.%)
	C ⁷	C ⁸					
<u>7</u>	hydroxy	hydroxy	8	72 ^a	113-115	1.52 (6H, s, 2CH ₃), 2.74 (2H, s, CH ₂), 5.85 (2H, br s, OH), 7.52 (1H, s, 5-H)	242 (M ⁺ , 33), 227 (54), 186 (100), 158 (11)
<u>8a</u>	methoxy	methoxy	2	23 ^b	70-71	1.53 (6H, s, 2CH ₃), 2.72 (2H, s, CH ₂), 3.91 (3H, s, CH ₃ O), 4.02 (3H, s, CH ₃ O), 7.67 (1H, s, 5-H)	270 (M ⁺ , 62), 255 (100), 215 (96), 186 (50), 171 (22)
<u>9a</u>	hydroxy	methoxy	2	50 ^b	174-175	1.52 (6H, s, 2CH ₃), 2.75 (2H, s, CH ₂), 4.02 (3H, s, CH ₃ O), 5.61 (1H, br s, OH), 7.47 (1H, s, 5-H)	256 (M ⁺ , 62), 241 (93), 201 (100), 182 (52), 154 (53)
<u>8b</u>	ethoxy	ethoxy	2	24	oil	1.40 (6H, m, 2CH ₃ -CH ₂ O), 1.52 (6H, s, 2CH ₃), 2.72 (2H, s, CH ₂), 4.11 (2H, q, J = 7 Hz, CH ₃ -CH ₂ O), 4.25 (2H, q, J = 7 Hz, CH ₃ -CH ₂ O), 7.65 (1H, s, 5-H)	295 (M ⁺ , 89), 283 (100), 243 (76), 215 (39), 186 (76), 170 (55), 157 (45), 83 (70)
<u>9b</u>	hydroxy	ethoxy	2	52 ^b	148-150	1.45 (3H, t, J = 7 Hz, CH ₃ -CH ₂ O), 1.50 (6H, s, 2CH ₃), 2.75 (2H, s, CH ₂), 4.27 (2H, q, J = 7 Hz, CH ₃ -CH ₂ O), 5.75 (1H, br s, OH), 7.47 (1H, s, 5-H)	270 (M ⁺ , 53), 255 (68), 227 (28), 215 (45), 186 (100), 170 (32), 157 (17)
<u>8c</u>	sec- butoxy	sec- butoxy	2	16	oil	1.00 (6H, m, 2CH ₃ -CH ₂ -CH-CH ₃), 1.25 (6H, m, 2CH ₃ CH ₂ -CH-CH ₃), 1.51 (6H, s, 2CH ₃), 1.51-1.91 (4H, m, 2CH ₃ CH ₂ -CH -CH ₃), 2.70 (2H, s, CH ₂), 4.28 (1H, m, CH ₃ CH ₂ -CH-CH ₃), 4.66 (1H, m, CH ₃ CH ₂ - -CH-CH ₃), 2.65 (1H, s, 5-H)	354 (M ⁺ , 7), 242 (45), 227 (100), 186 (57), 157 (10), 83 (15)
<u>9c</u>	hydroxy	sec- butoxy	2	45 ^b	95-97	1.03 (3H, t, J = 6 Hz, CH ₃ CH ₂ -CH-CH ₃), 1.31 (3H, d, J = 6 Hz, CH ₃ CH ₂ -CH-CH ₃), 1.50 (6H, s, 2CH ₃), 1.50-1.95 (2H, m, CH ₃ CH ₂ -CH-CH ₃), 2.75 (2H, s, CH ₂), 4.61 (1H, m, CH ₃ CH ₂ -CH-CH ₃), 5.55 (1H, br s, OH), 7.47 (1H, s, 5-H)	298 (M ⁺ , 9), 242 (30), 227 (100), 186 (88), 157 (9)
<u>8d</u>	cyclo- pentyl- oxy	cyclo- pentyl- oxy	2	15	oil	1.51 (6H, s, 2CH ₃), 1.55-2.02 (16H, m, 2x(CH ₂) ₄ =CH-), 2.70 (2H, s, CH ₂), 4.85 (1H, m, (CH ₂) ₄ =CH-), 5.15 (1H, m, (CH ₂) ₄ =CH-), 7.65 (1H, s, 5-H)	378 (M ⁺ , 4), 310 (2), 242 (55), 227 (100), 186 (57), 69 (24), 41 (58)
<u>9d</u>	hydroxy	cyclo- pentyl- oxy	2	50 ^b	113-115	1.51 (6H, s, 2CH ₃), 1.50-2.03 (8H, m, (CH ₂) ₄ =CH-), 2.75 (2H, s, CH ₂), 5.17 (1H, m, (CH ₂) ₄ =CH-), 5.57 (1H, br s, OH), 7.48 (1H, s, 5-H)	310 (M ⁺ , 5), 291 (12), 276 (30), 261 (34), 242 (38), 227 (100)

Table 1 (Contd.)

Compound	Substituent on		Reaction time ^c (h)	Yield (%)	mp (°C)	¹ H nmr (CDCl ₃) (ppm)	EIMS ^d (rel.int.%)
	C ^A	C ^B					
<u>10a</u>	ethoxy	methoxy	1	90 ^b	40	1.42 (3H, t, J = 7 Hz, CH ₃ -CH ₂ O), 1.52 (6H, s, 2CH ₃), 2.72 (2H, s, CH ₂), 4.03 (3H, s, CH ₃ O), 4.13 (2H, q, J = 7 Hz, CH ₃ -CH ₂ O), 7.67 (1H, s, 5-H)	284 (M ⁺ , 81), 269 (100), 241 (19), 229 (85), 213 (31), 201 (42), 182 (37)
<u>10b</u>	methoxy	ethoxy	1	92 ^b	31-32	1.45 (3H, t, J = 7 Hz, CH ₃ -CH ₂ O), 1.53 (6H, s, 2CH ₃), 2.73 (2H, s, CH ₂), 3.91 (3H, s, CH ₃ O), 4.25 (2H, q, J = 7 Hz, CH ₃ -CH ₂ O), 7.67 (1H, s, 5-H)	284 (M ⁺ , 83), 269 (100), 241 (30), 229 (70), 228 (32), 201 (64), 172 (59)
<u>10c</u>	methoxy	cyclo- pentyl- oxy	1	87 ^b	40	1.53 (6H, s, 2CH ₃), 1.50-2.05 (8H, m (CH ₂) ₄ =CH-), 2.72 (2H, s, CH ₂), 3.87 (3H, s, CH ₃ O), 5.12 (1H, m, (CH ₂) ₄ =CH-), 7.67 (1H, s, 5-H)	324 (M ⁺ , 8), 256 (38), 241 (100), 201 (62), 200 (29), 172 (29), 171 (20)
<u>8e</u>	propargyl- oxy	propargyl- oxy	3	85 ^b	oil	1.52 (6H, s, 2CH ₃), 2.56 (2H, m, 2CH=C-CH ₂ O), 2.73 (2H, s, CH ₂), 4.85 (2H, d, J = 2.5 Hz, CH=C- -CH ₂ O) 7.70 (1H, s, 5-H)	318 (M ⁺ , 25), 303 (10), 279 (38), 223 (28), 83 (40), 29 (100)

^aYield of the purified product, recrystallized from 50 % ethanol.

^bYield of the purified product, recrystallized from ethanol.

^cAveraged times, based on tlc monitoring of the reaction.

^d70 eV, direct inlet.

In a similar synthetic sequence, pyrogallol (4) was transformed to the bis-*tert*-butyl derivative (11)¹⁵. This compound was then cyclized to the dihydroxy-2,2-dimethyl-4-chromanone (12). Regioselective O-alkylation resulted in the formation of (14 a-e). The corresponding dialkoxy compounds (13 a-e) were also formed. It is worthy of note, however, that the regioselectivity was opposite to that, observed in the 6-chloro series and 6-*tert*-butyl-7-alkoxy-8-hydroxy-2,2-dimethyl-4-chromanone derivatives (14 a-e) were obtained (Scheme 2, Table 2). Further alkylation gave the corresponding novel dialkoxychromanones (15 a-e). Selected dialkoxychromanones were then reduced and dehydrated to the corresponding precocene analogues (16 a-f) (Scheme 3, Table 3).

Scheme 2

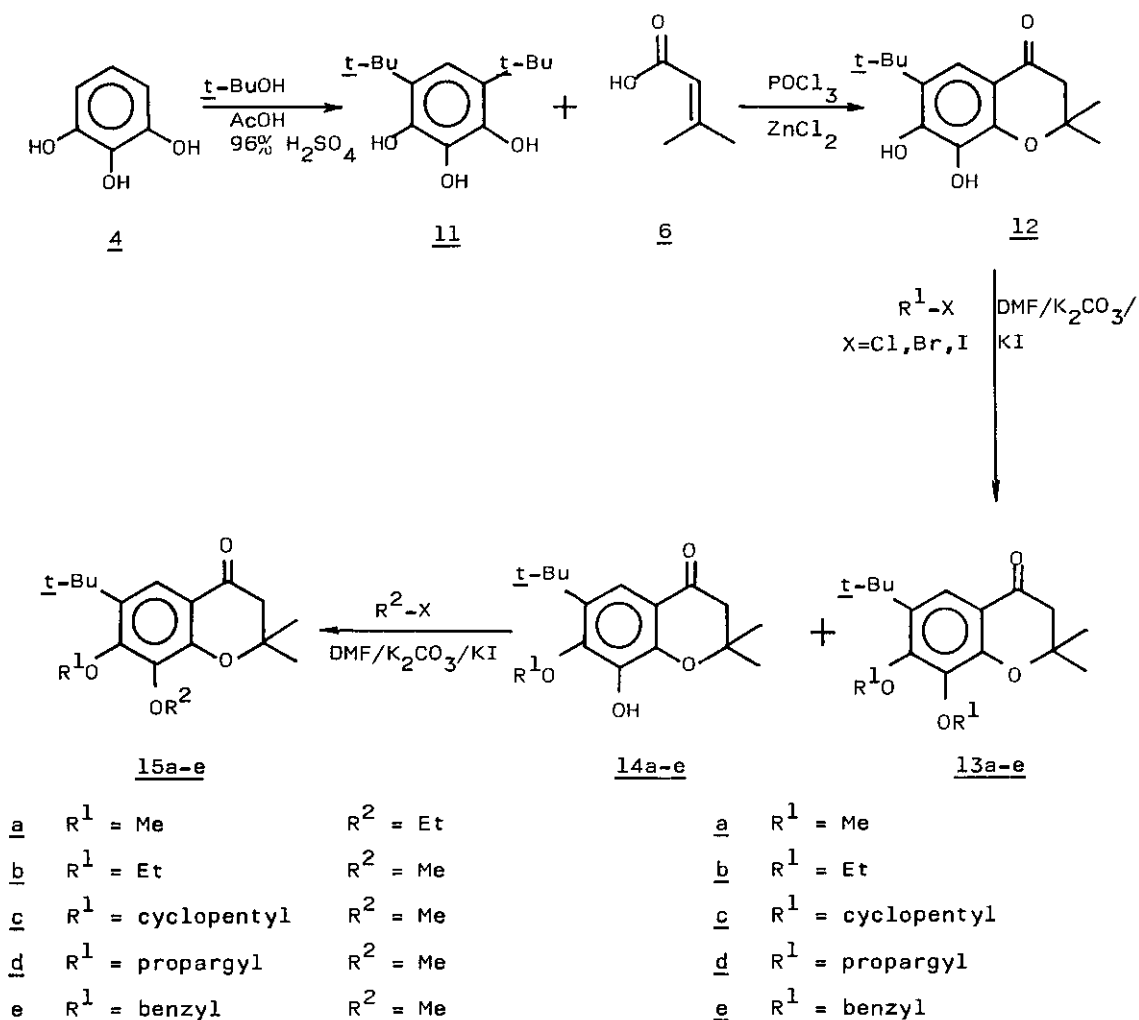


Table 2

Compound	Substituent on Reaction			Yield (%)	mp (°C)	¹ H nmr (CDCl ₃)	EIMS ^d (rel.int.%)
	C ⁷	C ⁸	time ^c (h)				
<u>12</u>	hydroxy	hydroxy	6	70 ^b	158-160	1.38 (9H, s, (CH ₃) ₃ C-), 1.47 (6H, s, 2CH ₃), 2.70 (2H, s, CH ₂), 5.82 (1H, br s, OH), 6.26 (1H, s, OH), 7.42 (1H, s, 5-H)	264 (M ⁺ , 50), 249 (100), 238 (14), 223 (82), 209 (62), 208 (45)
<u>13a</u>	methoxy	methoxy	0.5	77 ^b	79-80	1.35 (9H, s, (CH ₃) ₃ C-), 1.51 (6H, s, 2CH ₃), 2.69 (2H, s, CH ₂), 3.85 (3H, s, CH ₃ O), 4.01 (3H, s, CH ₃ O), 7.57 (1H, s, 5-H)	292 (M ⁺ , 40), 277 (58), 237 (38), 221 (100), 208 (18)
<u>14a</u>	methoxy	hydroxy	0.5	13 ^b	140-142	1.38 (9H, s, (CH ₃) ₃ C-), 1.51 (6H, s, 2CH ₃), 2.70 (2H, s, CH ₂), 3.97 (3H, s, CH ₃ O), 6.73 (1H, s, OH), 7.57 (1H, s, 5-H)	278 (M ⁺ , 55), 263 (100), 223 (37), 207 (55), 194 (13)
<u>13b</u>	ethoxy	ethoxy	0.5	79 ^b	124-126	1.35 (9H, s, (CH ₃) ₃ C-), 1.39 (3H, t, J = 7 Hz, CH ₃ -CH ₂ O), 1.44 (3H, t, J = 7 Hz, CH ₃ -CH ₂ O), 1.50 (6H, s, 2CH ₃), 2.67 (2H, s, CH ₂), 4.03 (2H, q, J = 7 Hz, CH ₃ -CH ₂ O), 4.30 (2H, q, J = 7 Hz, CH ₃ -CH ₂ O), 7.57 (1H, s, 5-H)	320 (M ⁺ , 54), 305 (63), 265 (33), 249 (100), 221 (18)
<u>14b</u>	ethoxy	hydroxy	0.5	9 ^b	127-129	1.38 (9H, s, (CH ₃) ₃ C-), 1.41 (3H, t, J = 7 Hz, CH ₃ -CH ₂ O), 1.50 (6H, s, 2CH ₃), 2.68 (2H, s, CH ₂), 4.20 (2H, q, J = 7 Hz, CH ₃ -CH ₂ O), 6.73 (1H, s, OH), 7.57 (1H, s, 5-H)	292 (M ⁺ , 63), 277 (100), 237 (35), 221 (41), 193 (17)
<u>13c</u>	cyclopentyl-oxy	cyclopentyl-oxy	0.5	76 ^b	120-122	1.35 (9H, s, (CH ₃) ₃ C-), 1.50 (6H, s, 2CH ₃), 1.42-2.02 (16H, m, 2x (CH ₂) ₄ =CH-), 2.65 (2H, s, CH ₂), 4.65 (1H, m, (CH ₂) ₄ =CH-), 5.68 (1H, m, (CH ₂) ₄ =CH-), 7.56 (1H, s, 5-H)	400 (M ⁺ , 4), 316 (5), 274 (10), 249 (38), 233 (30), 191 (90), 41 (100)
<u>14c</u>	cyclopentyl-oxy	hydroxy	0.5	14 ^b	147-149	1.37 (9H, s, (CH ₃) ₃ C-), 1.48 (6H, s, 2CH ₃), 1.56-1.97 (8H, m, (CH ₂) ₄ =CH-), 2.67 (2H, s, CH ₂), 5.02 (1H, m, (CH ₂) ₄ =CH-), 6.66 (1H, s, OH), 7.55 (1H, s, 5-H)	332 (M ⁺ , 27), 317 (2), 264 (63), 249 (100), 208 (63)
<u>13d</u>	propargyl-oxy	propargyl-oxy	0.5	79 ^b	75-76	1.38 (9H, s, (CH ₃) ₃ C-), 1.50 (6H, s, 2CH ₃), 2.50 (1H, m, CH≡C-CH ₂ O), 2.54 (1H, m, CH≡C-CH ₂ O), 4.73 (2H, d, J = 2.5 Hz, CH≡C-CH ₂ O), 4.97 (2H, d, J = 2.5 Hz, CH≡C-CH ₂ O), 7.62 (1H, s, 5-H)	340 (M ⁺ , 49), 325 (21), 301 (100), 284 (29), 269 (26), 245 (63)

Table 2 (contd.)

Compound	Substituent on		Reaction time ^c (h)	Yield (%)	mp (°C)	¹ H nmr (CDCl ₃)	EIMS ^d (rel.int.%)
	C ⁷	C ⁸					
<u>14d</u>	propargyl- oxy	hydroxy	0.5	14 ^b	105-107	1.38 (9H, s, (CH ₃) ₃ C-), 1.50 (6H, s, 2CH ₃), 2.51 (1H, t, J = 2.5 Hz, CH=C-CH ₂ O), 2.68 (2H, s, CH ₂), 4.82 (2H, d, J = 2.5 Hz, CH=C-CH ₂ O), 6.72 (1H, s, OH), 7.60 (1H, s, 5-H)	302 (M ⁺ , 60), 287 (42), 263 (98), 231 (11), 207(100)
<u>13e</u>	benzyl- oxy	benzyl- oxy	0.5	65 ^b	93-95	1.36 (9H, s, (CH ₃) ₃ C-), 1.47 (6H, s, 2CH ₃), 2.69 (2H, s, CH ₂), 4.97 (2H, s, Ar-CH ₂ O), 5.28 (2H, s, Ar-CH ₂ O), 7.21-7.47 (10H, m, Ar-protons), 7.62 (1H, s, 5-H)	444 (M ⁺ , 4), 353 (5), 297 (5), 150 (1), 91 (100)
<u>14e</u>	benzyl- oxy	hydroxy	0.5	16 ^b	149-151	1.32 (9H, s, (CH ₃) ₃ C-), 1.52 (6H, s, 2CH ₃), 2.70 (2H, s, CH ₂), 5.11 (2H, s, Ar-CH ₂ O), 6.50 (1H, s, OH), 7.39 (5H, m, Ar-protons), 7.57 (1H, s, 5-H)	354 (M ⁺ , 7), 298 (8), 263 (3), 207 (6), 91 (100)
<u>15a</u>	methoxy	ethoxy	1	92 ^b	121-123	1.37 (9H, s, (CH ₃) ₃ C-), 1.46 (3H, t, J = 7 Hz, CH ₃ -CH ₂ O), 1.51 (6H, s, 2CH ₃), 2.69 (2H, s, CH ₂), 3.83 (3H, s, CH ₃ O), 4.29 (2H, q, J = 7 Hz, CH ₃ -CH ₂ O), 7.57 (1H, s, 5-H)	306 (M ⁺ , 84), 251 (42), 235(100), 221 (11), 207 (28)
<u>15b</u>	ethoxy	methoxy	1	89 ^b	87-88	1.35 (9H, s, (CH ₃) ₃ C-), 1.41 (3H, t, J = 7 Hz, CH ₃ -CH ₂ O), 1.51 (6H, s, 2CH ₃), 2.68 (2H, s, CH ₂), 4.00 (3H, s, CH ₃ O), 4.04 (2H, q, J = 7 Hz, CH ₃ -CH ₂ O), 7.57 (1H, s, 5-H)	306 (M ⁺ , 79), 291 (79), 235(100), 221 (8), 207 (16)
<u>15c</u>	cyclo- pentyl- oxy	methoxy	1	87 ^b	48-50	1.35 (9H, s, (CH ₃) ₃ C-), 1.51 (6H, s, 2CH ₃), 1.06-2.06 (8H, m, (CH ₂) ₄ =CH-), 2.68 (2H, s, CH ₂), 3.97 (3H, s, CH ₃ O), 4.75 (1H, m, (CH ₂) ₄ =CH-), 7.57 (1H, s, 5-H)	346 (M ⁺ , 31), 278 (69), 263(100) 223 (50), 207 (38)
<u>15d</u>	propargyl- oxy	methoxy	1	90	oil	1.34 (9H, s, (CH ₃) ₃ C-), 1.51 (6H, s, 2CH ₃), 2.48 (1H, t, J = 2.5 Hz, CH=C-CH ₂ O), 2.70 (2H, s, CH ₂), 4.03 (3H, s, CH ₃ O), 4.72 (2H, d, J = 2 Hz, CH=C-CH ₂ O), 7.60 (1H, s, 5-H)	316 (M ⁺ , 58), 301 (16), 277(100), 221 (42), 193 (98)
<u>15e</u>	benzyl- oxy	methoxy	1	86 ^b	88-90	1.34 (9H, s, (CH ₃) ₃ C-), 1.45 (6H, s, 2CH ₃), 2.66 (2H, s, CH ₂), 4.01 (3H, s, CH ₃ O), 4.98 (2H, s, Ar-CH ₂ O), 7.27-7.52 (5H, m, Ar-protons), 7.57 (1H, s, 5-H)	368 (M ⁺ , 22), 312 (12), 277 (49), 221 (22), 91 (100)

a, b, c, d - See Table 1

Scheme 3

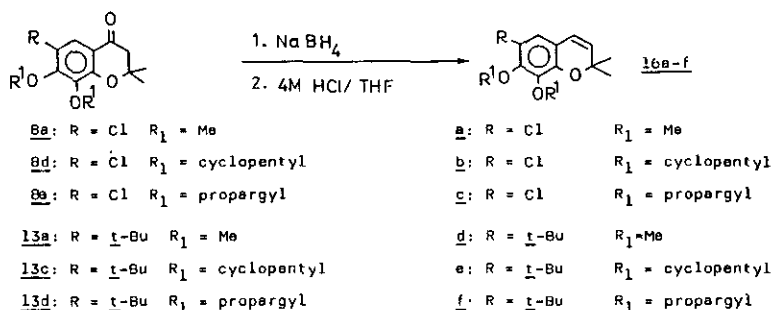


Table 3

Compound	R	R ¹	Reduction time		Yield (%)	¹ H nmr (CDCl ₃) (ppm)	EIMS (rel.int.%)
			Red. (h)	Dehydr. (h)			
<u>16a</u>	chloro	Methyl	0.5	1	78	1.47 (6H, s, 2CH ₃), 3.89 (3H, s, CH ₃ O), 3.90 (3H, s, CH ₃ O), 5.60 (1H, d, J = 10 Hz, 3-H), 6.20 (1H, d, J = 10 Hz, 4-H), 6.76 (1H, s, 5-H)	254 (M ⁺ , 23), 239 (100), 224 (13), 41 (23)
<u>16b</u>	chloro	cyclopentyl	0.5	2	85	1.45 (6H, s, 2CH ₃), 1.50-2.05 (16H, m, 2x(CH ₂) ₄ =CH-), 4.85 (1H, m, (CH ₂) ₄ =CH-), 4.98 (1H, m, (CH ₂) ₄ =CH-), 5.55 (1H, d, J = 10 Hz, 3-H), 6.20 (1H, d, J = 10 Hz, 4-H), 6.73 (1H, s, 5-H)	362 (M ⁺ , 6), 294 (8), 279 (5), 226 (15), 211 (100)
<u>16c</u>	chloro	propargyl	0.5	2.5	76	1.47 (6H, s, 2CH ₃), 2.50 (2H, m, 2CH=C-CH ₂ O), 4.80 (4H, m, 2CH=C-CH ₂ O), 5.60 (1H, d, J = 10 Hz, 3-H), 6.20 (1H, d, J = 10 Hz, 4-H), 6.79 (1H, s, 5-H)	302 (M ⁺ , 91), 287 (100), 263 (24), 248 (14), 209 (29), 181 (20)
<u>16d</u>	tert-butyl	methyl	2.5	1	76	1.32 (9H, s, (CH ₃) ₃ C-), 1.46 (6H, s, 2CH ₃), 3.85 (3H, s, CH ₃ O), 3.91 (3H, s, CH ₃ O), 5.50 (1H, d, J = 10 Hz, 3-H), 6.25 (1H, d, J = 10 Hz, 4-H), 6.62 (1H, s, 5-H)	276 (M ⁺ , 54), 261 (100), 231 (18), 187 (10)
<u>16e</u>	tert-butyl	cyclopentyl	2.5	1.5	80	1.33 (9H, s, (CH ₃) ₃ C-), 1.44 (6H, s, 2CH ₃), 1.50-2.03 (16H, m, 2x(CH ₂) ₄ =CH-), 4.72 (1H, m, (CH ₂) ₄ =CH-), 5.43 (1H, d, J = 10 Hz, 3H), 5.55 (1H, m, (CH ₂) ₄ =CH-), 6.23 (1H, d, J = 10 Hz, 4-H), 6.62 (1H, s, 5-H)	384 (M ⁺ , 98), 326 (31), 301 (68), 248 (42), 233 (100), 217 (29)
<u>16f</u>	tert-butyl	propargyl	1.5	2	87	1.36 (9H, s, (CH ₃) ₃ C-), 1.45 (6H, s, 2CH ₃), 2.51 (2H, m, 2CH=C-CH ₂ O), 4.73 (2H, d, J = 2.5 Hz, CH=C-CH ₂ O), 4.83 (2H, d, J = 2.5 Hz, CH=C-CH ₂ O), 5.51 (1H, d, J = 10 Hz, 3-H), 6.23 (1H, d, J = 10 Hz, 4-H), 6.66 (1H, s, 5-H)	324 (M ⁺ , 47), 309 (100), 285 (23), 231 (31), 203 (28)

Determination of the substitution pattern of various chromanone derivatives

J-echo ^{13}C -spectra^{16,17} were recorded for selected chromanones (3 a-e), since the information provided by the ^1H -spectra proved to be insufficient for the determination of substitution patterns.

There are well-known empirical chemical shift rules for the ^{13}C -spectra of chromanones¹⁸ and substituted aromatic compounds^{18,19}. These rules were used in the determination of the substitution pattern of the molecules under investigation (Table 5). It was possible to complete the assignment in the case of 12. This helped us to determine the expected δ_{c} values for the unsubstituted compound and obtain a Z_1 correction factor for the effects of the pyranone ring. Thus, the C-5 - C-8 chemical shifts can be calculated as follows:

$$\delta_{\text{C}_1} = 128.5 + \sum_{k=5}^8 Q_k$$

$$Z_5 = -5.8, \quad Z_6 = -6.9, \quad Z_7 = +8.3, \quad Z_8 = -13.3$$

The Q_k correction factors are known from the literature¹⁸. In order to corroborate a particular ^{13}C assignment an arbitrary prescription was put to good use. The difference between the measured and calculated ^{13}C chemical shifts was not allowed to be higher than 5 ppm. Table 4 shows for 3b and 3d that a hypothetical exchange of the R^7 and R^8 substituents would give a ca. 10 ppm difference between the calculated and measured chemical shifts which is clearly in contradiction with our "thumb rule".

Table 4 Measured-calculated ^{13}C shifts for 3b and 3d

	$(\delta_{\text{m}} - \delta_{\text{c}})_{\underline{3b}}$	R^7 and R^8 reversed	$(\delta_{\text{m}} - \delta_{\text{c}})_{\underline{3d}}$	R^7 and R^8 reversed
C-5	-1.8	-1.8	+4.2	+4.2
C-6	+2.8	+4.3	+4.7	+3.0
C-7	-0.8	-7.0	+3.0	+9.2
C-8	+5.4	+11.6	+1.6	-4.6

Table 5 ^{13}C nmr shifts of selected chromanones 3a-e

Compound	R ₆	R ₇	R ₈	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-8a	C-4a	2-CH ₃
<u>3a</u>	chloro	hydroxy	hydroxy	79.95	47.99	189.92	116.20	114.04 ^a	148.26 ^b	134.63	148.26 ^b	113.10 ^b	26.06
<u>3b</u>	chloro	hydroxy	methoxy	80.13	47.70	190.11	114.99	119.09 ^a	148.85 ^b	140.65	148.66 ^b	116.26 ^a	25.81
<u>3c</u>	tert-butyl	hydroxy	hydroxy	79.23	48.11	190.34	113.77	132.40	147.54	128.98	151.55	111.54	26.11
<u>3d</u>	tert-butyl	methoxy	hydroxy	79.49	47.76	189.99	117.62	135.35	155.31	129.29	151.40	111.92	26.06
<u>3e</u>	tert-butyl	methoxy	methoxy	79.65	47.69	190.62	116.92	134.56	158.34	141.45	152.43	115.02	25.94

a, b - These assignments can be reversed

Bioactivity data of these novel analogues of the natural precocenes will be reported elsewhere.

EXPERIMENTAL

Melting points were determined on a PHMK hot stage melting point apparatus and are uncorrected. Microanalyses were performed in the Microanalysis Department of Kossuth Lajos University. Mass spectra were obtained on a VG 7035 mass spectrometer in the EI mode 70 eV, 170 °C. 200.13 MHz ^1H nmr spectra were recorded with a BRUKER WP 200 SY nmr spectrometer. Following a 45 degree ($3\mu\text{s}$) pulse data were accumulated in 16K memory giving 0.24 Hz/pt digital resolution. Internal TMS was used as reference standard. The 50.3 MHz ^{13}C nmr spectra were obtained by the use of the same spectrometer. Usually a J-modulated spin-echo spectrum was recorded for each of the compounds in order to establish the number of attached protons for a particular carbon atom¹⁶. Typically 4-6 sec relaxation delay was allowed between the sequences. According to an average $^1\text{J}_{\text{CH}} = 150$ Hz coupling $1/\text{J} = 6.6$ msec delay has been inserted into the spin-echo sequence. Broadband decoupled ^{13}C nmr spectra were obtained in 16K memory, giving ca. 1.2 Hz/pt digital resolution. Chemical shifts were referenced to the solvent signal of DMSO- d_6 as 39.5 ppm.

4-Chloropyrogallol (5)

This compound was obtained by the method of Horner and Gówecke¹⁴. The product was recrystallized from benzene, yield:81%. mp 163-164°C (lit.¹⁴ 86%, mp 153-156°C)

4,6-Bis-tert-butylpyrogallol (11)

This compound was synthesized by the method of Schulze and Flaig¹⁵. The product was recrystallized from benzene, 91%. mp 120-121 °C (lit.¹⁵ 94%, mp 121 °C).

6-Chloro-7,8-dihydroxy-2,2-dimethyl-4-chromanone (7) and 6-tert-butyl-7,8-dihydroxy-2,2-dimethyl-4-chromanone (12)

To a stirred mixture of POCl_3 (1290g, 750 ml, 8.4 moles) and 3-methylbut-2-enoic acid (6) (55g, 0.55 mole) were added 102 g. (0.75 mole) of ZnCl_2 and 0.5 mole of 4-chloropyrogallol (5) or 4,6-bis-tert-butylpyrogallol (11). The reaction mixture was stirred at room temperature, then poured onto crushed ice 2000 g and stirred for further 4 h. The separated solid was filtered off, washed with cold water to remove acidic contaminants and the crude products were recrystallized from 50% ethanol. Reaction times and other data are given in Table 1 and 2.

O-Alkylation of dihydroxy-2,2-dimethyl-4-chromanones

The chromanone (7 or 12) (20 mmoles) was dissolved in DMFA (50 ml) and stirred with K_2CO_3 (8.29g, 60 mmoles), KI (0.2 g) and an alkylating agent (60 mmoles) at 80 °C. When the starting material disappeared on tlc, the mixture was poured onto crushed ice (200g). A 5% solution of NaOH (50 ml) was then added and the mixture was extracted twice with diethyl ether (2x50 ml). The organic layer was then washed with cold water (3x50 ml), dried over anhydrous Na_2SO_4 and evaporated in vacuum. The residue (8 or 13) was crystallized from ethanol or purified by column chromatography on silica gel Kieselgel 60, hexane:diethyl ether = 9 : 1 as eluent.

The alkylane aqueous solution was acidified with conc. HCl to pH 1 at or below 5 °C, and the precipitate (9 or 14) was filtered off, washed with cold water, and recrystallized from ethanol. The latter compounds were subsequently O-alkylated as described above. Reaction times and other data are in Table 1 and 2.

Reduction and dehydration of dialkoxy-2,2-dimethyl-4-chromanones

The corresponding chromanone (8 or 13) (15 mmoles) was dissolved in methanol (50 ml) and stirred at room temperature for the time given in Table 3 during with $NaBH_4$ (2.83g, 75 mmoles) was added into the reaction mixture in portions. The solvent was removed in vacuum, 50 ml of water was added and extraction was performed with dichloromethane (3x25 ml). The combined dichloromethane solution was washed with cold water (3x25 ml), dried over anhydrous Na_2SO_4 and evaporated in vacuum. The residue was dissolved in tetrahydrofuran (25 ml) and stirred with 4 M HCl solution (30 ml) at room temperature. Reaction times for each chromenes are given in Table 3. The reaction mixture was subsequently extracted with diethyl ether (3x25 ml), and the combined organic layers were washed with 2 % solution of NaOH (2x25 ml), water (3x25 ml), brine (2x25 ml), dried over Na_2SO_4 and evaporated in vacuum. Analytical samples were obtained by column chromatography on silica gel Kieselgel 60, hexane:diethyl ether = 9:1 was used as eluent. Other data are given in Table 3.

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