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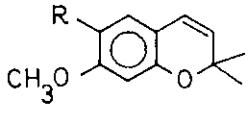
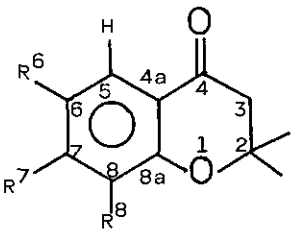
Abstract - The synthesis of novel benzopyran compounds 16 a-f, analogues of the natural precocenes (1 and 2) is described. These derivatives are obtained via novel synthesis and regioselective O-alkylation of 6-chloro- and 6-tert-butyl-7,8-dihydroxy-2,2-dimethyl-4-chromanones (7 and 12).

Precocenes (1 and 2) are known inhibitors of juvenile hormone biosynthesis in susceptible insects[1-3]. These compounds are of natural origin, isolated from Ageratum houstonianum[4] 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 QSAR[9] in the case of these new synthetic precocene analogues. Our test media were the migratory locust Locusta migratoria[10] and the nematode Caenorhabditis remanei[11,12].



1 R = H Precocene 1
2 R = CH_3O Precocene 2

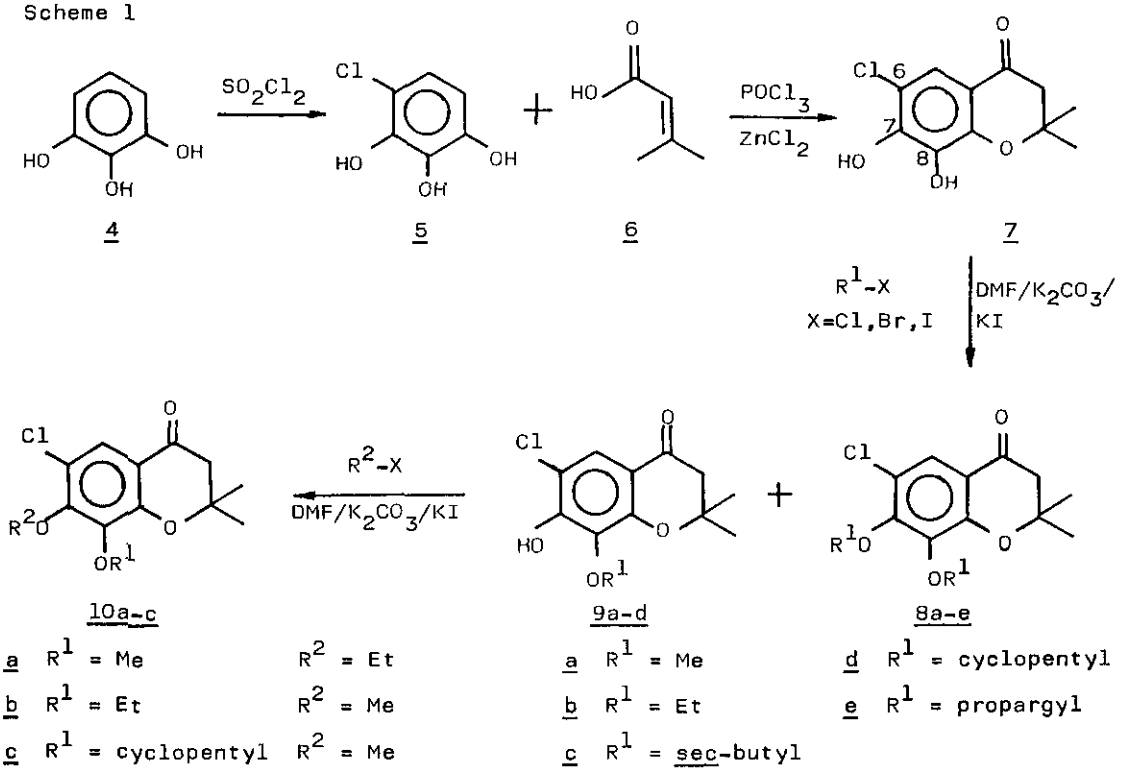
On the basis of our earlier results[13], we required 6- chloro- and 6-tert - butyl-7,8-dialkoxy-2,2-dimethyl-2H-chromenes (16 a-f). In this paper we describe high-yield syntheses of these novel precocene analogues from common intermediates of 3-type.



3a-e

Thus, 4-chloropyrogallol (5) was synthesized by the method of Horner and Gowecke[14] (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



4 5 6 7

10a-c

a	R^1 = Me	R^2 = Et
b	R^1 = Et	R^2 = Me
c	R^1 = cyclopentyl	R^2 = Me

9a-d

a	R^1 = Me
b	R^1 = Et
c	R^1 = sec-butyl

8a-e

d	R^1 = cyclopentyl
e	R^1 = propargyl

Table 1

Compound	Substituent on C[7]	Substituent on C[8]	Reaction time[c] (h)	Yield (%)	mp (°C)	^{1}H nmr ($CDCl_3$) (ppm)	EIMS[d] (rel.int.%)
7	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, 5H)	242 (M^+,33), 227 (54), 186 (100), 158 (11)
8a	methoxy	methoxy	2	23[b]	70-71	1.53 (6H, s, $2CH_3$), 2.72 (2H, s, CH_2), 3.91 (3H, s, CH_3O), 4.02 (3H, s CH_3O), 7.67 (1H s 5-H)	270 (M^+,62), 255 (100), 215 (96), 186 (50), 171 (22),
9a	hydroxy	methoxy	2	50[b]	174-175	1.52 (6H s, $2CH_3$), 2.75 (2H, s, CH_2), 4.02 (3H, s, CH_3O), 5.61 (1H,br s,OH), 7.47 (1H, s, 5-H)	256 (M^+, 62), 241 (93), 201 (100), 182 (52), 154 (53)
8b	ethoxy	ethoxy	2	24	oil	1.40 (6H, m, $2CH_3$-CH_2O), 1.52 (6H, s, $2CH_3$) 2.72 (2H s, CH_2), 4.11 (2H, q, J = 7 Hz, CH_3-CH_2O), 4.25 (2H, q, J = 7 Hz, CH_3-CH_2O), 7.65 (1H, s, 5-H)	295 (M^+,89), 283 (100), 243 (76) 215 (39), 186 (76), 170 (55), 157 (45), 83 (70)
9b	hydroxy	ethoxy	2	52[b]	148-150	1.45 (3H, t, J = 7Hz, CH_3-CH_2O), 1.50 (6H, s, $2CH_3$), 2.75 (2H, s, CH_2),4.27 (2H q J = 7 Hz, CH_3-CH_2O), 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)
8c	sec-butoxy	sec-butoxy	2	16	oil	1.00 (6H, m, $2CH_3$-CH_2-CH-CH_3), 1.25 (6H m, $2CH_3CH_2$-CH-CH_3), 1.51 (6H, s, $2CH_3$), 1.51-1.91 (4H, m, $2CH_3CH_2$-CH -CH_3) 2.70 (2H, s, CH_2), 4.28 (1H, m, CH_3CH_2-CH-CH_3), 4.66 (1H, m, CH_3CH_2-CH -CH_3) 2.65 (1H, s, 5-H)	354 (M^+, 7), 242 (45), 227 (100), 186 (57), 157 (10), 83 (15)
9c	hydroxy	sec-butoxy	2	45[b]	95-97	1.03 (3H, t J = 6 Hz, CH_3CH_2-CH-CH_3), 1.31 (3H, d, J = 6 Hz CH_3CH_2-CH-CH_3), 1.50 (6H s $2CH_3$), 1.50-1.95 (2H, m, CH_3CH_2-CH-CH_3), 2.75 (2H, s, CH_2), 4.61 (1H, m, CH_3CH_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)
8d	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 (68)
9d	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 C[7]	Substituent on C[8]	Reaction time[c] (h)	Yield (%)	mp (°C)	^{1}H nmr ($CDCl_3$) (ppm)	EIMS[d] (rel.int.%)
10a	ethoxy	methoxy	1	90[b]	40	1.42 (3H, t, J = 7Hz, CH_3-CH_2O), 1.52 (6H, s, $2CH_3$), 2.72 (2H, s, CH_2), 4.03 (3H, s, CH_3O), 4.13 (2H, q, J = 7 Hz, CH_3-CH_2O), 7.67 (1H, s, 5-H)	284 (M^+, 81), 269 (100), 241 (19), 229 (85), 213 (31), 201 (42), 182 (37)
10b	methoxy	ethoxy	1	92[b]	31-32	1.45 (3H, t, J = 7 Hz, CH_3-CH_2O), 1.53 (6H, s, $2CH_3$), 2.73 (2H, s, CH_2), 3.91 (3H, s, CH_3O), 4.25 (2H, q, J = 7 Hz CH_3-CH_2O), 7.67 (1H, s, 5-H)	284 (M^+, 83), 269 (100), 241 (30), 229 (70), 228 (32), 201 (64), 172 (59)
10c	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_3O), 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)
8e	propargyl-oxy	propargyl-oxy	3	85[b]	oil	1.52 (6H, s, $2CH_3$), 2.56 (2H, m, $2CH$≡C-CH_2O), 2.73 (2H s, CH_2), 4.85 (2H d, J = 2.5 Hz, CH≡C--CH_2O) 7.70 (1H s, 5-H)	318 (M^+, 25), 303 (10), 279 (38), 223 (28), 83 (40), 29 (100)

[a] Yield of the purified product, recrystallized from 50 % ethanol.

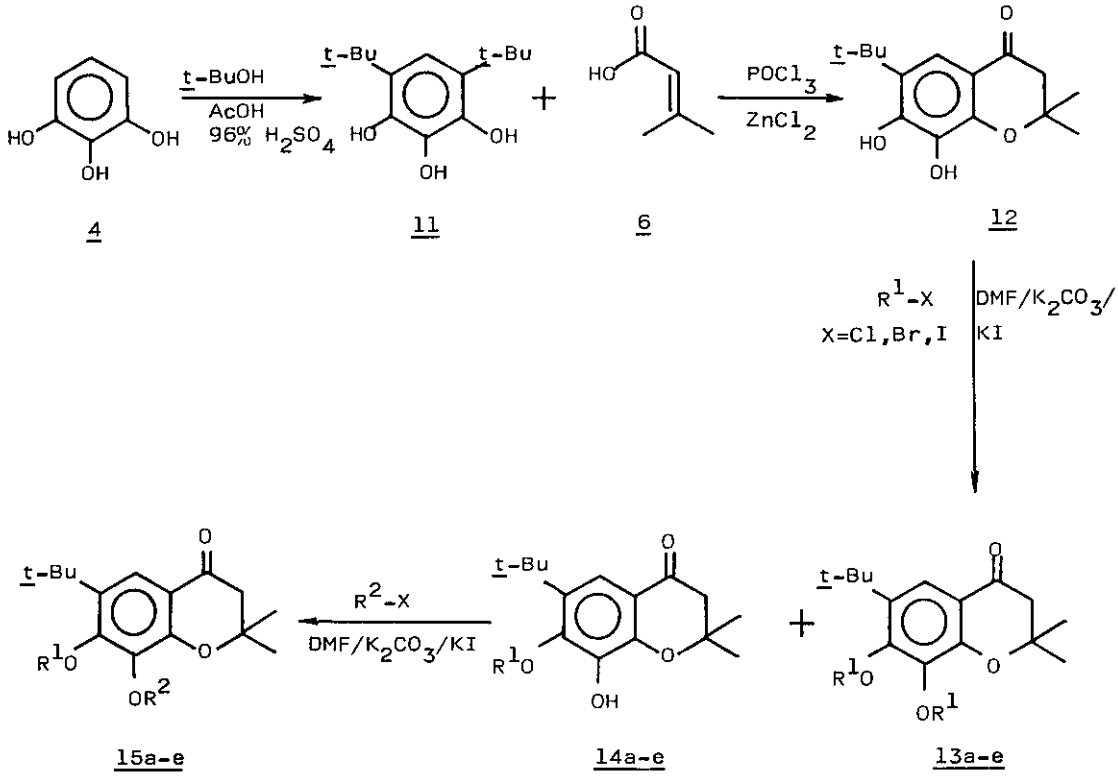
[b] Yield of the purified product, recrystallized from ethanol.

[c] Averaged times, based on tlc monitoring of the reaction.

[d] 70 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



4 11 6 12

15a-e 14a-e 13a-e

a	R^1 = Me	R^2 = Et	a	R^1 = Me
b	R^1 = Et	R^2 = Me	b	R^1 = Et
c	R^1 = cyclopentyl	R^2 = Me	c	R^1 = cyclopentyl
d	R^1 = propargyl	R^2 = Me	d	R^1 = propargyl
e	R^1 = benzyl	R^2 = Me	e	R^1 = benzyl

Table 2

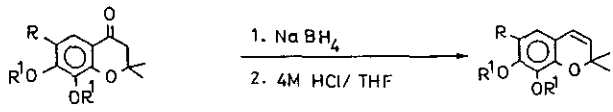
Compound	Substituent on C[7]	Substituent on C[8]	Reaction time[c] (h)	Yield (%)	mp (°C)	^{1}H nmr ($CDCl_3$)	EIMS[d] (rel.int.%)
12	hydroxy	hydroxy	6	70[a]	158-160	1.38 (9H, s, $(CH_3)_3C$-), 1.47 (6H, s, $2CH_3$), 2.70 (2H, s, CH_2), 5.82 (1H, br s, OH), 6.26 (1H, s, OH), 7.42 (1H, s, 5-H)	264 (M^+, 50), 249 (100), 238 (14), 223 (82), 209 (62), 208 (45)
13a	methoxy	methoxy	0.5	77[b]	79-80	1.35 (9H, s, $(CH_3)_3C$-), 1.51 (6H, s, $2CH_3$), 2.69 (2H, s, CH_2), 3.85 (3H, s, CH_3O), 4.01 (3H, s, CH_3O), 7.57 (1H, s, 5-H)	292 (M^+, 40), 277 (58), 237 (38), 221 (100), 208 (18)
14a	methoxy	hydroxy	0.5	13[b]	140-142	1.38 (9H, s, $(CH_3)_3C$-), 1.51 (6H, s, $2CH_3$), 2.70 (2H, s, CH_2), 3.97 (3H, s, CH_3O), 6.73 (1H, s, OH), 7.57 (1H, s, 5-H)	278 (M^+, 55), 263 (100), 223 (37), 207 (55), 194 (13)
13b	ethoxy	ethoxy	0.5	79[b]	124-126	1.35 (9H, s, $(CH_3)_3C$-), 1.39 (3H, t, J = 7 Hz, CH_3-CH_2O), 1.44 (3H, t, J = 7 Hz, CH_3-CH_2O), 1.50 (6H, s, $2CH_3$), 2.67 (2H, s, CH_2), 4.03 (2H, q, J = 7 Hz, CH_3-CH_2O), 4.30 (2H, q, J = 7 Hz, CH_3-CH_2O), 7.57 (1H, s, 5-H)	320 (M^+, 54), 305 (63), 265 (33), 249 (100), 221 (18)
14b	ethoxy	hydroxy	0.5	9[b]	127-129	1.38 (9H, s, $(CH_3)_3C$-), 1.41 (3H, t, J = 7 Hz, CH_3-CH_2O), 1.50 (6H, s, $2CH_3$), 2.68 (2H, s, CH_2), 4.20 (2H, q, J = 7 Hz, CH_3-CH_2O), 6.73 (1H, s, OH), 7.57 (1H, s, 5-H)	292 (M^+, 63), 277 (100), 237 (35), 221 (41), 193 (17)
13c	cyclopentyloxy	cyclopentyloxy	0.5	76[b]	120-122	1.35 (9H, s, $(CH_3)_3C$-), 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)
14c	cyclopentyloxy	hydroxy	0.5	14[b]	147-149	1.37 (9H, s, $(CH_3)_3C$-), 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)
13d	propargyloxy	propargyloxy	0.5	79[b]	75-76	1.38 (9H, s, $(CH_3)_3C$-), 1.50 (6H, s, $2CH_3$), 2.50 (1H, m, CH≡C-CH_2O), 2.54 (1H, m, CH≡C-CH_2O), 4.73 (2H, d, J = 2.5 Hz, CH≡C-CH_2O), 4.97 (2H, d, J = 2.5 Hz, CH≡C-CH_2), 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 C7	Substituent on C8	Reaction time[c] (h)	Yield (%)	mp (°C)	^{1}H nmr ($CDCl_3$)	EIMS[d] (rel.int.%)
14d	propargyl-oxy	hydroxy	0.5	14[b]	105-107	1.38 (9H, s, $(CH_3)_3C$-), 1.50 (6H, s, $2CH_3$), 2.51 (1H, t, J = 2.5 Hz, CH≡C-CH_2O), 2.68 (2H, s, CH_2), 4.82 (2H, d, J = 2.5 Hz, CH≡C-CH_2O), 6.72 (1H, s, OH), 7.60 (1H, s, 5-H)	302 (M^+, 60), 287 (42), 263 (98), 231 (11), 207(100)
13e	benzyl-oxy	benzyl-oxy	0.5	65[b]	93-95	1.36 (9H, s, $(CH_3)_3C$-), 1.47 (6H, s, $2CH_3$), 2.69 (2H, s, CH_2), 4.97 (2H, s, Ar-CH_2O), 5.28 (2H, s, Ar-CH_2O), 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)
14e	benzyl-oxy	hydroxy	0.5	16[b]	149-151	1.32 (9H, s, $(CH_3)_3C$-), 1.52 (6H, s, $2CH_3$), 2.70 (2H, s, CH_2), 5.11 (2H s, Ar-CH_2O), 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)
15a	methoxy	ethoxy	1	92[b]	121-123	1.37 (9H, s, $(CH_3)_3C$-), 1.46 (3H, t, J = 7 Hz, CH_3-CH_2O), 1.51 (6H, s, $2CH_3$), 2.69 (2H, s, CH_2), 3.83 (3H, s, CH_3O), 4.29 (2H, q, J = 7 Hz, CH_3-CH_2O), 7.57 (1H, s, 5-H)	306 (M^+, 84), 251 (42), 235(100), 221 (11), 207 (28)
15b	ethoxy	methoxy	1	89[b]	87-88	1.35 (9H,s, $(CH_3)_3C$-), 1.41 (3H, t, J = 7 Hz, CH_3-CH_2O), 1.51 (6H, s, $2CH_3$), 2.68 (2H, s, CH_2), 4.00 (3H, s, CH_3O), 4.04 (2H, q, J = 7 Hz, CH_3-CH_2O), 7.57 (1H, s, 5-H)	306 (M^+, 79), 291 (79), 235(100), 221 (8), 207 (16)
15c	cyclo-pentyl-oxy	methoxy	1	87[b]	48-50	1.35 (9H, s, $(CH_3)_3C$-), 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_3O), 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)
15d	propargyl-oxy	methoxy	1	90	oil	1.34 (9H, s, $(CH_3)_3C$-), 1.51 (6H, s, $2CH_3$), 2.48 (1H, t, J = 2.5 Hz, CH≡ C-CH_2O), 2.70 (2H, s, CH_2), 4.03 (3H, s CH_3O), 4.72 (2H, d, J = 2 Hz, CH≡ C-CH_2O) 7.60 (1H, s, 5-H)	316 (M^+, 58), 301 (16), 277(100), 221 (42), 193 (98)
15e	benzyl-oxy	methoxy	1	86[b]	88-90	1.34 (9H, s, $(CH_3)_3C$-), 1.45 (6H, s, $2CH_3$), 2.66 (2H, s, CH_2), 4.01 (3H, s, CH_3O), 4.98 (2H, 3, Ar-CH_2O), 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



16a-f

8a: R = Cl R_1 = Me
8d: R = Cl R_1 = cyclopentyl
8e: R = Cl R_1 = propargyl

13a: R = t-Bu R_1 = Me
13c: R = t-Bu R_1 = cyclopentyl
13d: R = t-Bu R_1 = propargyl

a: R = Cl R_1 = Me
b: R = Cl R_1 = cyclopentyl
c: R = Cl R_1 = propargyl
d: R = t-Bu R_1 = Me
e: R = t-Bu R_1 = cyclopentyl
f: R = t-Bu R_1 = propargyl

Table 3

Compound	R	R^1	Reduction time Red. (h)	Dehidr. (h)	Yield (%)	^{1}H nmr ($CDCl_3$) (ppm)	EIMS (rel.int.%)
16a	chloro	Methyl	0.5	1	78	1.47 (6H, s, $2CH_3$), 3.89 (3H, s, CH_3O), 3.90 (3H, s., CH_3O), 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)
16b	chloro	cyclo-pentyl	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)
16c	chloro	propargyl	0.5	2.5	76	1.47 (6H, s, $2CH_3$), 2.50 (2H, m, $2CH\equiv C-CH_2O$), 4.80 (4H, m, $2CH\equiv C-CH_2O$), 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)
16d	tert-butyl	methyl	2.5	1	76	1.32 (9H, s, $(CH_3)_3C$), 1.46 (6H, s, $2CH_3$), 3.85 (3H, s, CH_3O), 3.91 (3H, s, CH_3O), 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)
16e	tert-butyl	cyclo-pentyl	2.5	1.5	80	1.33 (9H, s, $(CH_3)_3C$), 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)
16f	tert-butyl	propargyl	1.5	2	87	1.36 (9H, s, $(CH_3)_3C$), 1.45 (6H, s, $2CH_3$), 2.51 (2H, m, $2CH\equiv C-CH_2O$), 4.73 (2H, d, J = 2.5 Hz, $CH\equiv C-CH_2O$), 4.83 (2H, d, J = 2.5 Hz, $CH\equiv C-CH_2O$), 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 ^{1}H-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 chromanones[18] 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:

$$\delta C_1 = 128.5 + \sum_{k=5}^{8} Q_k$$

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

The Q_k correction factors are known from the literature[18]. In order to corroborate a particular ^{13}C assigment 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 substitutents 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 m-\delta c)$3b	R^7 and R^8 reversed	$(\delta m-\delta c)$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	
3a	chloro	hydroxy	hydroxy	79.95	47.99	189.92	116.20	114.04[a]	148.26[b]	134.63	148.26[b]	113.10[a]	26.06	
3b	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	O$\underline{C}H_3$=60.13
3c	tert-butyl	hydroxy	hydroxy	79.23	48.11	190.34	113.77	132.40	147.54	128.98	151.55	111.54	26.11	$\underline{C}(CH_3)_3$=33.80 C($\underline{C}H_3$)$_3$=29.68
3d	tert-butyl	methoxy	hydroxy	79.49	47.76	189.99	117.52	135.35	155.31	129.29	151.40	111.92	26.06	$\underline{C}(CH_3)_3$=33.91 C($\underline{C}H_3$)$_3$=29.15
3e	tert-butyl	methoxy	methoxy	79.65	47.69	190.62	116.92	134.56	158.34	141.45	152.43	115.02	25.94	$\underline{C}(CH_3)_3$=34.11 C($\underline{C}H_3$)$_3$=29.90

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 ^{1}H nmr spectra were recorded with a BRUKER WP 200 SY nmr spectrometer. Following a 45 degree (3 μs) 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 atom[16]. Typically 4-6 sec relaxation delay was allowed between the sequences. According to an average $^{1}J_{CH}$ = 150 Hz coupling 1/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 Gówecke[14]. 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 Flaig[15]. 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 dissapeared 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 alkilane 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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