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MODIFIED COUMARINS. 16. CYCLOHEXANE-ANNELATED ANALOGS OF PYRANOCOUMARINS

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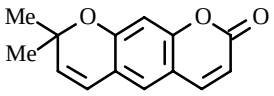
Modified derivatives of angular and linear pyranocoumarins containing a condensed cyclohexane moiety were prepared by fusing a 2,2-dimethyltetrahydropyran ring to the coumarin system and annelating a pyrone ring to derivatives of 2,2-dimethylchromane.

Key words: coumarins, pyranocoumarins, furocoumarins, chromanones, glycosides, glycosylation, 7,8,9,10-tetrahydrobenzo[*c*]chromen-6-one.

Pyranocoumarins are a widely distributed group of coumarins that contain a 2,2-dimethylpyran ring annelated to a benzopyran-2-one system [1]. Most natural pyranocoumarins are deivatives of the linear pyran xanthyletin (**1**) or its angular isomer seselin (**2**).



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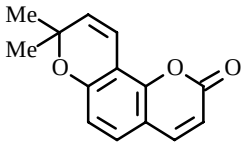

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Our goal was to synthesize modified analogs of pyranocoumarins that contain an annelated cyclohexane ring. Pyranocoumarins were synthesized by two methods: 1) fusing a 2,2-dimethylpyran ring to the coumarin system and 2) annelating a pyrone ring to a 2,2-dimethylchromane core.

3-Hydroxy-4-methyl- (**3**), 1-hydroxy-3-methyl- (**5**), and 3,4-dihydroxy-7,8,9,10-tetrahydrobenzo[*c*]chromen-6-one (**10**) that were necessary for further transformations were prepared by Pechmann condensation of 2-carbethoxycyclohexanone with 2-methylresorcinol, orcinol, and pyrogallol, respectively, in the presence of conc. H_2SO_4 at 0°C [2]. 3-Hydroxy-4-methylbenzo[*c*]chromen-6-one (**4**) was synthesized by the Hartley method by condensation of 2-bromobenzoic acid and 2-methylresorcinol in NaOH solution using copper sulfate solution (10%) as a catalyst [3].

Hydroxycoumarins **3**, **4**, and **5** were condensed with 3,3-dimethylallylbromide in the presence of *p*-toluenesulfonic acid [4] to give the linear dihydropuranocoumarins 7,9,9-trimethyl-1,2,3,4,10,11-hexahydrobenzo[*c*]pyrano[3,2-*g*]chromen-5-one (**6**), 7,9,9-trimethyl-10,11-dihydrobenzo[*c*]pyrano[3,2-*g*]chromen-5-one (**7**), and 2,2,5-trimethyl-3,4,9,11,12-hexahydrobenzo[*c*]pyrano[2,3-*f*]chromen-8-one (**9**).

The results were the same if the alkylating agent 3-methyl-2-buten-1-ol was used instead of 3,3-dimethylallylbromide. The PMR spectra of **6**, **7**, and **9** exhibit a broadened splitting pattern for the aromatic protons compared with the starting coumarins because of decoupling of H-6 of the benzopyran ring. Furthermore, PMR spectra of the resulting compounds have signals characteristic of the 2,2-dimethyltetrahydropyran ring [5].

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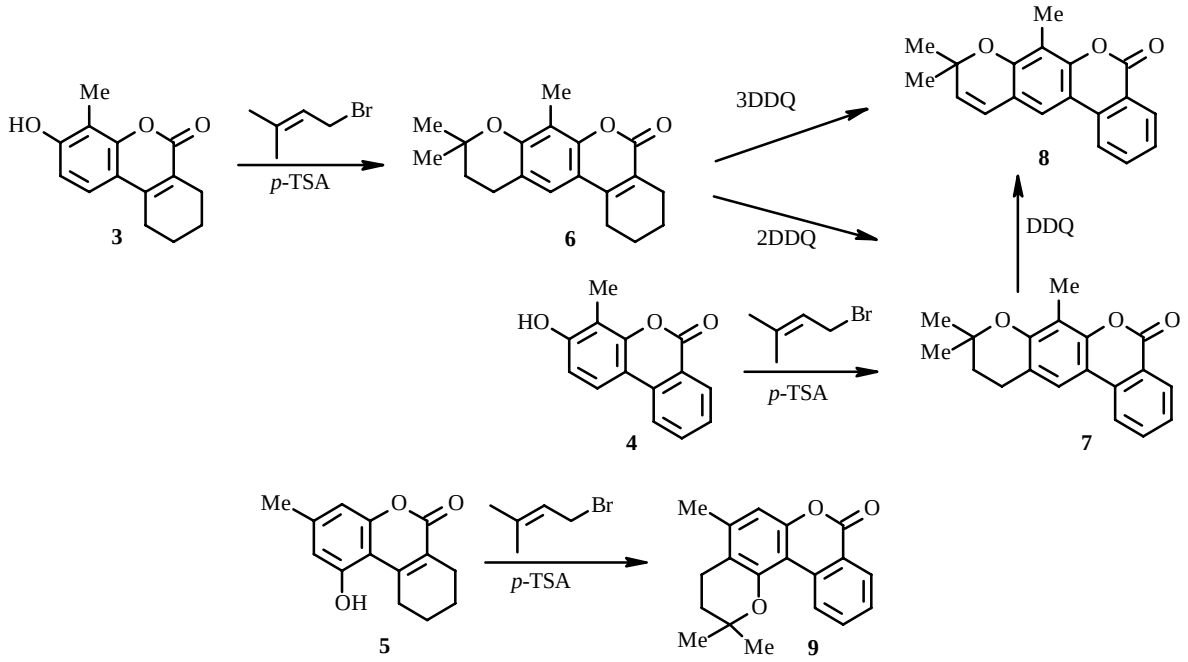
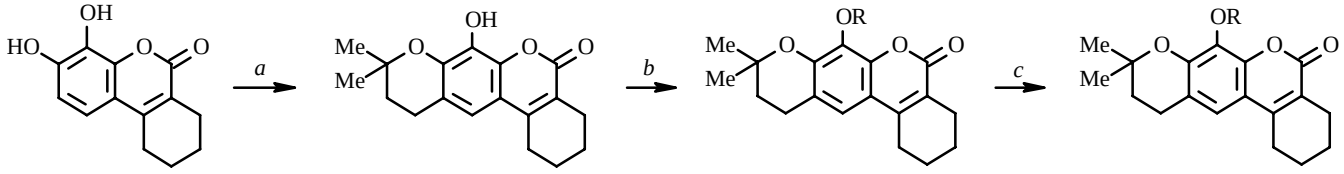


Treatment of **6** with two equivalents of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dioxane causes dehydrogenation primarily of the cyclohexane ring annelated to the coumarin system to give **7**. Reaction of **6** with three equivalents of DDQ in toluene leads to complete aromatization of the system to form 7,9,9-trimethylbenzo[*c*]pyrano[3,2-*g*]chromen-5-one (**8**). The PMR spectrum of **8** has two doublets at 5.71 and 6.43 ppm with SSCC J = 9.6 Hz that are typical of an annelated pyran ring [5]. It should be noted that **8** is also formed by aromatization of **7** using DDQ in toluene.

Condensation of **10** and 3,3-dimethylallylbromide in the presence of *p*-toluenesulfonic acid formed the linear dihydropyranocoumarin 7-hydroxy-9,9-dimethyl-1,2,3,4,10,11-hexahydrobenzo[*c*]pyrano[3,2-*g*]chromen-5-one (**11**). Hydroxydihydropyranocoumarin **11** was glycosylated by a modified Michael method [6]. Acetobromoglucose (Ac_4Glu*p*Br) or acetobromogalactose (Ac_4Gal*p*Br) and the potassium salt of **11** were condensed in aqueous acetone with cooling (0°C).



10 **11** **12, 13** **14, 15**

12: R = Ac_4Glu*p*
13: R = Ac_4Gal*p*

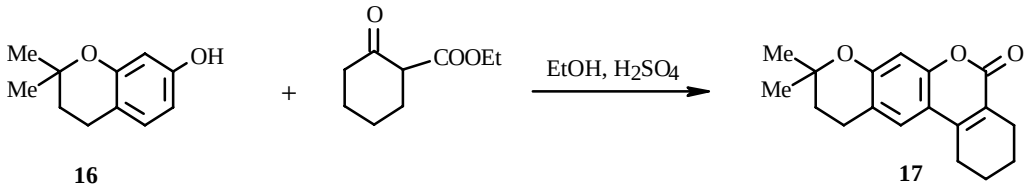
14: R = Glu*p*
15: R = Gal*p*

a. $(CH_3)_2CH{=}CHCH_2Br$, *p*-TSA; *b.* KOH, CH_3COCH_3-H_2O, Ac_4Gal*p*Br (or Ac_4Glu*p*Br); *c.* MeONa, MeOH

Signals for protons of the coumarin aglycons and carbohydrates were found unambiguously in PMR spectra of the synthesized tetra-O-acetylglycopyranosides **12** and **13**. The configuration of the anomeric center was determined using PMR spectroscopy. The presence in the spectra of a doublet for anomeric H-1′ at 5.14 ppm with SSCC J = 7.5 Hz (for glucoside **12**) and 5.05 ppm with SSCC J = 8.1 Hz (for galactoside **13**) is consistent with formation of a 1,2-*trans*-glycoside bond (β-configuration of the anomeric center) [7]. IR spectra of **12** and **13** have two bands at 1760-1730 and 1710-1715 cm^{-1} that are typical of C=O stretching vibrations of acetyls and coumarins, respectively.

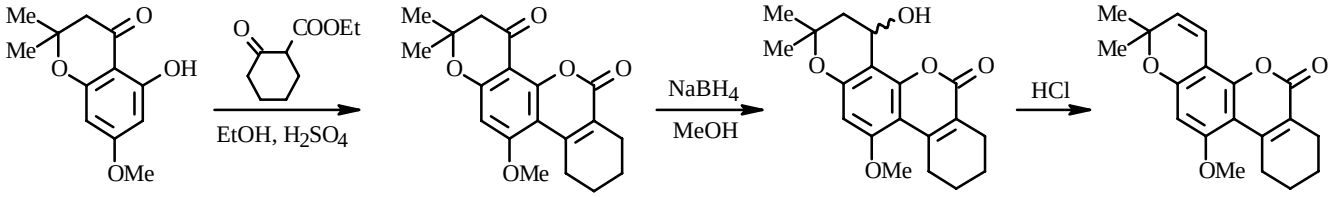
Deacetylation of **12** and **13** by a modified Zemplen method (NaOMe in MeOH) produced β-D-glycopyranosides **14** and **15** in high yields. PMR spectra of the synthesized glycosides contain signals for the carbohydrate and aglycon. In contrast with the starting peracetates, they lack signals for the acetyls. Retention of the β-configuration was confirmed by the presence in the PMR spectra of a doublet for anomeric H-1′ at 4.97 ppm with SSCC J = 7.2 Hz (for glucopyranoside **14**) and 4.96 ppm with SSCC J = 7.8 Hz (for galactopyranoside **15**). IR spectra of **14** and **15** have two bands at 3300-3400 and 1700-1710 cm^{-1} that are typical for stretching vibrations of alcohols and coumarin C=O bonds, respectively.

Pechmann condensation of 2,2-dimethylchroman-7-ol (**16**) and ethyl-2-oxocyclohexanecarboxylate in the presence of conc. H_2SO_4 produced 9,9-dimethyl-1,2,3,4,10,11-hexahydrobenzo[*c*]pyrano[3,2-*g*]chromen-5-one (**17**), a modified analog of the natural pyranocoumarin dihydroxanthyletin that contains an annelated cyclohexane moiety.



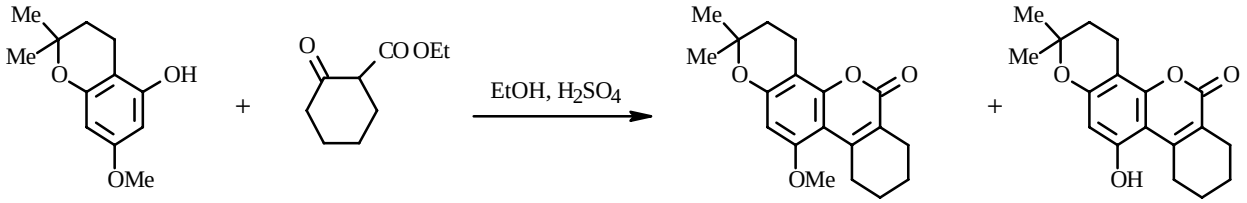
16 **17**

Pechmann condensation of 2,2-dimethyl-5-hydroxy-7-methoxy-4-chromanone (**18**) and ethyl-2-oxocyclohexanecarboxylate in the presence of conc. H_2SO_4 formed 11-methoxy-2,2-dimethyl-2,3,7,8,9,10-hexahydrobenzo[*c*]pyrano[2,3-*h*]chromen-4,6-dione (**19**). The PMR spectrum of **19** exhibits signals for the chromanone ring (6H singlet for two methyls and a singlet for the CH_2 protons), the cyclohexane moiety, and a 1H singlet for the aromatic protons. Reduction of **19** using $NaBH_4$ in CH_3OH produced chromanol **20**, dehydration of which under acid-catalysis conditions (HCl in dioxane) [8] produced 11-methoxy-2,2-dimethyl-7,8,9,10-tetrahydrobenzo[*c*]pyrano[2,3-*h*]chromen-6-one (**21**), a modified analog of the natural pyranocoumarin 5-methoxyseselin that contains an annelated cyclohexane moiety. The PMR spectrum of **21** contains two doublets at 5.70 and 6.61 ppm with SSCC J = 9.6 Hz that are typical of an annelated pyran ring [5].



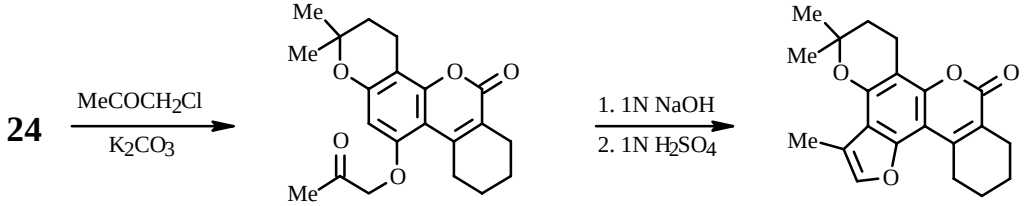
18 **19** **20** **21**

Pechmann condensation of 7-methoxy-5-hydroxy-2,2-dimethylchromane (**22**) and ethyl-2-oxocyclohexanecarboxylate in the presence of conc. H_2SO_4 led to partial demethoxylation of the reaction product to form a mixture of 11-methoxy-2,2-dimethyl-3,4,7,8,9,10-hexahydrobenzo[*c*]pyrano[2,3-*h*]chromen-6-one (**23**) and its 11-hydroxy derivative (**24**).



22 **23** **24**

11-Hydroxy-2,2-dimethyl-3,4,7,8,9,10-hexahydrobenzo[*c*]pyrano[2,3-*h*]chromen-6-one (**24**) was used as starting material to annelate a furan ring to the dihdyropyranocoumarin system. The MacLeod approach [9] was used to fuse the furan ring. Alkylation of **24** under Williamson reaction conditions using chloroacetone formed oxoester **25**, which cyclized smoothly on heating with NaOH solution (1 N) and subsequent acidolysis to 3,5,5-trimethyl-6,7,10,11,12,13-hexahydrobenzo[*c*]furo[2,3-*f*]pyrano[2,3-*h*]chromen-9-one (**26**).



25 **26**

EXPERIMENTAL

The course of reactions and purity of products were monitored using TLC on Merck 60 F254 plates with elution by $CHCl_3$:CH_3OH (9:1). Melting points were determined on a Kofler block. IR and UV spectra were measured on a Nicolet FTIR Nexus 475 spectrometer and Specord M40 spectrophotometer, respectively. PMR spectra were recorded on a Varian VXR-300 spectrometer at 300 MHz relative to TMS (internal standard). Elemental analyses of all compounds agreed with those calculated.

Syntheses of **3-5**, **16**, **18**, and **22** have been reported [2, 10, 11]. Acetobromoglycopyranosides were prepared as before [12].

7,9,9-Trimethyl-1,2,3,4,10,11-hexahydrobenzo[*c*]pyrano[3,2-*g*]chromen-5-one (6). A mixture of **3** (2.30 g, 10 mmol), 3,3-dimethylallylbromide (1.75 mL, 15 mmol) or 3-methyl-2-buten-1-ol (1.52 mL, 15 mmol), and *p*-toluenesulfonic acid monohydrate (1.90 g, 10 mmol) in toluene (50 mL) was held at 100-110°C for 24 h (completion of reaction was determined using TLC). After the reaction was complete, solvent was removed in vacuo in a rotary evaporator. The solid was dissolved in $CHCl_3$ (50 mL). The resulting solution was treated with NaOH solution (1 N, 2×50 mL) and saturated NaCl solution. Acidification of the combined alkaline solutions regenerated unreacted hydroxycoumarin. The organic layer was dried over anhydrous $MgSO_4$. Solvent was removed in vacuo in a rotary evaporator. The oily residue was crystallized from hexane, yield 68%, mp 135-136°C, $C_{19}H_{22}O_3$. IR spectrum (KBr, cm^{-1}): 2940, 1706, 1614, 1582, 1392, 1262, 1164, 1126.

UV spectrum (CH_3CN, λ_{max}, nm, log ε): 210 (4.69), 224 (4.26), 328 (4.24).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.36 (6H, s, two CH_3-9), 1.78 (4H, m, CH_2-2, CH_2-3), 1.83 (2H, t, J = 7.2, CH_2-10), 2.26 (3H, s, CH_3-7), 2.55 (2H, m, CH_2-4), 2.73 (2H, m, CH_2-1), 2.84 (2H, t, J = 7.2, CH_2-11), 7.11 (1H, s, H-12).

7,9,9-Trimethyl-10,11-dihydrobenzo[*c*]pyrano[3,2-*g*]chromen-5-one (7) was prepared analogously to **6** starting with **4** (2.26 g, 10 mmol), yield 74%, mp 142-143°C, $C_{19}H_{18}O_3$. IR spectrum (KBr, cm^{-1}): 1720, 1610, 1572, 1486, 1454, 1380, 1368, 1356, 1316, 1276, 1240, 1228, 1184, 1160, 1122, 1088.

UV spectrum (CH_3CN, λ_{max}, nm, log ε): 212 (4.50), 226 (4.60), 286 (4.13), 311 (4.05).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.38 (6H, s, two CH_3-9), 1.86 (2H, t, J = 7.2, CH_2-10), 2.29 (3H, s, CH_3-7), 2.89 (2H, t, J = 7.2, CH_2-11), 7.44 (1H, t, J = 8.1, H-3), 7.59 (1H, s, H-12), 7.73 (1H, t, J = 8.1, H-2), 7.97 (1H, d, J = 8.1, H-4), 8.33 (1H, d, J = 8.1, H-1).

7,9,9-Trimethyl-10,11-dihydrobenzo[c]pyrano[3,2-*g*]chromen-5-one (7). A solution of **6** (0.60 g, 2 mmol) in dioxane (5 mL) was treated with a solution of DDQ (0.91 g, 4 mmol) in dioxane (5 mL) and heated for 6 h (completion of reaction was determined using TLC). After the reaction was complete, the solid hydroquinone was filtered off. Solvent was removed in vacuo in a rotary evaporator. The oily residue was crystallized from hexane:propan-2-ol (2:1), yield 54%.

7,9,9-Trimethylbenzo[*c*]pyrano[3,2-*g*]chromen-5-one (8). A solution of **7** (0.59 g, 2 mmol) in toluene (10 mL) was treated with a solution of DDQ (0.68 g, 3 mmol) in toluene (10 mL) and held at 100°C for 8 h (completion of reaction was determined using TLC). After the reaction was complete, the solid hydroquinone was filtered off. Solvent was removed in vacuo in a rotary evaporator. The solid was dissolved in $CHCl_3$ (50 mL) and treated with NaOH solution (1 N, 2×50 mL) and saturated NaCl solution. The organic phase was dried over anhydrous $MgSO_4$. Solvent was removed in vacuo in a rotary evaporator. The oily residue was crystallized from propan-2-ol, yield 72%, mp 150-151°C, $C_{19}H_{16}O_3$. IR spectrum (KBr, cm^{-1}): 1728, 1616, 1444, 1378, 1320, 1280, 1186, 1158, 1124.

UV spectrum (CH_3CN, λ_{max}, nm, log ε): 210 (4.37), 257 (4.57), 265 (4.55), 288 (3.93), 344 (4.00).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.44 (6H, s, two CH_3-9), 2.32 (3H, s, CH_3-7), 5.71 (1H, d, J = 9.6, H-10), 6.43 (1H, d, J = 9.6, H-11), 7.48 (1H, t, J = 8.1, H-3), 7.50 (1H, s, H-12), 7.76 (1H, t, J = 8.1, H-2), 7.98 (1H, d, J = 8.1, H-4), 8.35 (1H, d, J = 8.1, H-1).

7,9,9-Trimethylbenzo[*c*]pyrano[3,2-*g*]chromen-5-one (8) was also produced in 65% yield starting with **6** (0.60 g, 2 mmol) and DDQ (1.82 g, 8 mmol).

2,2,5-Trimethyl-3,4,9,10,11,12-hexahydrobenzo[*c*]pyrano[2,3-*f*]chromen-8-one (9) was prepared analogously to **6** starting with **5** (2.30 g, 10 mmol), yield 75%, mp 141-142°C, $C_{19}H_{22}O_3$. IR spectrum (KBr, cm^{-1}): 2928, 1698, 1606, 1452, 1416, 1404, 1388, 1168, 1148, 1114, 1088.

UV spectrum (CH_3CN, λ_{max}, nm, log ε): 208 (4.54), 304 (4.16).

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.34 (6H, s, two CH_3-2), 1.69 (4H, m, CH_2-10, CH_2-11), 1.82 (2H, t, J = 7.2, CH_2-3), 2.23 (3H, s, CH_3-5), 2.40 (2H, m, CH_2-9), 2.62 (2H, t, J = 7.2, CH_2-4), 3.06 (2H, m, CH_2-12), 6.64 (1H, s, H-6).

3,4-Dihydroxy-7,8,9,10-tetrahydrobenzo[*c*]chromen-6-one (10). A cooled (0°C) solution of pyrogallol (12.6 g, 0.1 mol) and ethyl-2-oxocyclohexanecarboxylate (16.0 mL, 0.1 mol) in EtOH (20 mL) was vigorously stirred and cooled and treated dropwise with conc. H_2SO_4 (10 mL). The reaction mixture was stirred until it thickened, after which it was left overnight at room temperature. The mixture was poured into icewater (250 mL). The resulting precipitate was filtered off and crystallized from CH_3CN, yield 86%, mp 259-260°C (lit. 269-276°C [13], 276°C [14]), $C_{13}H_{12}O_4$. IR spectrum (KBr, cm^{-1}): 3468, 2940, 1704, 1680, 1612, 1584, 1512, 1384, 1330, 1204, 1098.

UV spectrum (EtOH, λ_{max}, nm, log ε): 203 (4.76), 264 (4.25), 324 (4.39).

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.70-1.80 (4H, m, CH_2-8, CH_2-9), 2.38 (2H, m, CH_2-10), 2.70 (2H, m, CH_2-7), 6.77 (1H, d, J = 8.7, H-2), 7.00 (1H, d, J = 8.7, H-1), 9.35 and 9.94 (2H, two br.s, OH-3, OH-4).

7-Hydroxy-9,9-dimethyl-1,2,3,4,10,11-hexahydrobenzo[*c*]pyrano[3,2-*g*]chromen-5-one (11). A mixture of **10** (2.32 g, 10 mmol), 3,3-dimethylallylbromide (1.75 mL, 15 mmol), and *p*-toluenesulfonic acid monohdyrate (1.90 g, 10 mmol) in toluene (50 mL) was held at 100-110°C for 24 h (completion of reaction was determined using TLC). After the reaction was complete, solvent was removed in vacuo in a rotary evaporator. The oily residue was crystallized from propan-2-ol, yield 43%, mp 204-205°C, $C_{18}H_{20}O_4$. IR spectrum (KBr, cm^{-1}): 3432, 2932, 1710, 1690, 1628, 1582, 1468, 1398, 1368, 1274, 1124.

UV spectrum (EtOH, λ_{max}, nm, log ε): 211 (4.86), 266 (4.31), 331 (4.43).

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.31 (6H, s, two CH_3-9), 1.71 (4H, m, CH_2-2, CH_2-3), 1.78 (2H, t, J = 7.2, CH_2-10), 2.37 (2H, m, CH_2-4), 2.70 (2H, m, CH_2-1), 2.77 (2H, t, J = 7.2, CH_2-11), 6.90 (1H, s, H-12), 8.94 (1H, s, OH-7).

7-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyloxy)-9,9-dimethyl-1,2,3,4,10,11-hexahydrobenzo[*c*]pyrano[3,2-*g*]chromen-5-one (12). A solution of **11** (1.50 g, 5 mmol) in acetone (5 mL) and KOH solution (2.8 mL, 10%, 5 mmol) was stirred vigorously and cooled (0°C) for 30 min. Acetobromoglucose (2.06 g, 5 mmol) was added in portions with stirring over 1 h. The resulting solution was stirred for 4 h with cooling (0°C) and left overnight at room temperature. The reaction mixture was diluted with $CHCl_3$ (25 mL) and treated successively in a separatory funnel with KOH solution (1 N, 2×25 mL) and water (25 mL). The organic phase was dried over anhydrous $MgSO_4$. Solvent was removed in vacuo in a rotary evaporator. The oily residue was crystallized from propan-2-ol, yield 49%, mp 116-117°C, $C_{32}H_{38}O_{13}$. IR spectrum (KBr, cm^{-1}): 1760, 1732, 1712, 1680, 1618, 1460, 1388, 1224, 1124, 1048.

UV spectrum (EtOH, λ_{max}, nm, log ε): 210 (4.74), 328 (4.25).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.33, 1.40 (6H, two s, two CH_3-9), 1.75-1.90 (6H, m, CH_2-2, CH_2-3, CH_2-10), 2.02, 2.04, 2.16 (12H, three s, four CH_3COO), 2.54 (2H, m, CH_2-4), 2.70 (2H, m, CH_2-1), 2.83 (2H, t, J = 7.2, CH_2-11), 3.64 (1H, m, H-5′), 4.10 (1H, dd, J = 12.0, J = 2.4, H-6′α), 4.21 (1H, dd, J = 12.0, J = 5.7, H-6′β), 5.14 (1H, d, J = 7.5, H-1′), 5.23-5.32 (2H, m, H-2′, H-3′), 5.41 (1H, dd, J = 9.9, J = 9.6, H-4′), 7.05 (1H, s, H-12).

7-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyloxy)-9,9-dimethyl-1,2,3,4,10,11-hexahydrobenzo[*c*]pyrano[3,2-*g*]chromen-5-one (13) was prepared analogously to **12** starting with **11** (1.50 g, 5 mmol) and acetobromogalactose (2.06 g, 5 mmol), yield 54%, mp 143-144°C, $C_{32}H_{38}O_{13}$. IR spectrum (KBr, cm^{-1}): 1752, 1728, 1710, 1614, 1574, 1484, 1460, 1372, 1228, 1158, 1124, 1078.

UV spectrum (EtOH, λ_{max}, nm, log ε): 210 (4.73), 328 (4.30).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.35, 1.42 (6H, two s, two CH_3-9), 1.70-1.90 (6H, m, CH_2-2, CH_2-3, CH_2-10), 1.97, 2.01, 2.18, 2.22 (12H, four s, four CH_3COO), 2.54 (2H, m, CH_2-4), 2.71 (2H, m, CH_2-1), 2.84 (2H, t, J = 7.2, CH_2-11), 3.82 (1H, t, J = 6.9, H-5′), 4.11 (2H, d, J = 7.2, CH_2-6′), 5.05 (1H, d, J = 8.1, H-1′), 5.08 (1H, dd, J = 8.1, J = 3.3, H-3′), 5.41 (1H, d, J = 3.3, H-4′), 5.59 (1H, dd, J = 8.1, J = 8.1, H-2′), 7.06 (1H, s, H-12).

7-(β-D-Glucopyranosyloxy)-9,9-dimethyl-1,2,3,4,10,11-hexahydrobenzo[*c*]pyrano[3,2-*g*]chromen-5-one (14). A solution of **12** peracetate (1.26 g, 2 mmol) in absolute MeOH (10 mL) was treated with NaOMe (50 mg). The reaction mixture was boiled for 30 min (completion of reaction was determined using TLC). The precipitate that formed on cooling (0°C) was filtered off and washed with cold MeOH, yield 91%, mp 235-236°C, $C_{24}H_{30}O_9$. IR spectrum (KBr, cm^{-1}): 3364, 2928, 1704, 1680, 1612, 1576, 1460, 1392, 1124, 1064.

UV spectrum (EtOH, λ_{max}, nm, log ε): 211 (4.65), 328 (4.21).

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.31, 1.36 (6H, two s, two CH_3-9), 1.65-1.84 (6H, m, CH_2-2, CH_2-3, CH_2-10), 2.39 (2H, m, CH_2-4), 2.73 (2H, m, CH_2-1), 2.82 (2H, t, J = 7.2, CH_2-11), 3.06 (1H, m, H-4′), 3.19 (2H, m, H-2′, H-3′), 3.27-3.42 (2H, m, H-5′, H-6′α), 3.55 (1H, dd, J = 11.7, J = 5.4, H-6′β), 4.27 (1H, t, J = 5.6, OH-6), 4.97 (1H, d, J = 7.2, H-1′), 5.06 (1H, d, J = 4.5, OH), 5.17 (1H, d, J = 4.2, OH), 5.20 (1H, d, J = 4.5, OH), 7.19 (1H, s, H-12).

7-(β-D-Galactopyranosyloxy)-9,9-dimethyl-1,2,3,4,10,11-hexahydrobenzo[*c*]pyrano[3,2-*g*]chromen-5-one (15) was prepared analogously to **14** starting with **13** (1.26 g, 2 mmol), yield 87%, mp 184-185°C, $C_{24}H_{30}O_9$. IR spectrum (KBr, cm^{-1}): 3408, 2932, 1708, 1690, 1612, 1574, 1484, 1462, 1392, 1158, 1122, 1072.

UV spectrum (EtOH, λ_{max}, nm, log ε): 210 (4.61), 328 (4.16).

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.34, 1.41 (6H, two s, two CH_3-9), 1.70-1.90 (6H, m, CH_2-2, CH_2-3, CH_2-10), 2.41 (2H, m, CH_2-4), 2.73 (2H, m, CH_2-1), 2.83 (2H, t, J = 7.2, CH_2-11), 3.15-3.70 (6H, m, H-2′, H-3′, H-4′, H-5′, CH_2-6′), 4.25 (1H, t, J = 5.6, OH-6), 4.37 (1H, d, J = 4.5, OH), 4.67 (1H, d, J = 4.2, OH), 4.76 (1H, d, J = 4.5, OH), 4.96 (1H, d, J = 7.8, H-1′), 7.13 (1H, s, H-12).

9,9-Dimethyl-1,2,3,4,10,11-hexahydrobenzo[*c*]pyrano[3,2-*g*]chromen-5-one (17). A solution of **16** (0.89 g, 5 mmol) and ethyl-2-oxocyclohexanecarboxylate (0.8 mL, 5 mmol) in EtOH (5 mL) was vigorously stirred and treated dropwise with conc. H_2SO_4 (5 mL). The reaction mixture was left overnight at room temperature and poured into icewater (50 mL). The resulting precipitate was filtered off and crystallized from propan-2-ol, yield 78%, mp 145-146°C, $C_{18}H_{20}O_3$. IR spectrum (KBr, cm^{-1}): 1712, 1620, 1570, 1498, 1392, 1306, 1156, 1112.

UV spectrum (EtOH, λ_{max}, nm, log ε): 207 (4.67), 222 (4.22), 329 (4.25).

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.29 (6H, s, two CH_3-9), 1.98 (4H, m, CH_2-2, CH_2-3), 1.79 (2H, t, J = 7.2, CH_2-10), 2.34 (2H, m, CH_2-4), 2.68 (2H, m, CH_2-1), 2.78 (2H, t, J = 7.2, CH_2-11), 6.62 (1H, s, H-7), 7.38 (1H, s, H-12).

11-Methoxy-2,2-dimethyl-2,3,7,8,9,10-hexahydrobenzo[*c*]pyrano[2,3-*h*]chromen-4,6-dione (19). A solution of **18** (2.22 g, 10 mmol) and ethyl-2-oxocyclohexanecarboxylate (1.60 mL, 10 mmol) in EtOH (5 mL) was treated dropwise with conc. H_2SO_4 (10 mL). The reaction mixture was held at 50°C for 8 h, left overnight at room temperature, and poured into icewater (100 mL). The resulting precipitate was filtered off and crystallized from propan-2-ol, yield 56%, mp 213-214°C, $C_{19}H_{20}O_5$. IR spectrum (KBr, cm^{-1}): 1710, 1690, 1612, 1574, 1468, 1382, 1262, 1236, 1204, 1110.

UV spectrum (CH_3CN, λ_{max}, nm, log ε): 218 (4.53), 284 (4.44), 311 (4.32).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 1.47 (6H, s, two CH_3-2), 1.72 (4H, m, CH_2-8, CH_2-9), 2.54 (2H, m, CH_2-10), 2.72 (2H, s, CH_2-3), 3.00 (2H, m, CH_2-7), 3.91 (3H, s, CH_3O-11), 6.26 (1H, s, H-12).

4-Hydroxy-11-methoxy-2,2-dimethyl-2,3,7,8,9,10-hexahydrobenzo[*c*]pyrano[2,3-*h*]chromen-4-one (20). A solution of **19** (1.31 g, 4 mmol) in MeOH (10 mL) was treated in portions with $NaBH_4$ (0.46 g, 12 mmol). The reaction mixture was held at room temperature and stirred vigorously for 2 h (completion of reaction was determined using TLC), poured into saturated NaCl solution (100 mL), and extracted with ethylacetate (3×20 mL). The organic phase was dried over anhydrous $MgSO_4$. Solvent was removed in vacuo in a rotary evaporator. The solid was crystallized from MeOH, yield 82%, mp 231-232°C, $C_{19}H_{22}O_5$. IR spectrum (KBr, cm^{-1}): 3393, 1712, 1620, 1588, 1480, 1432, 1388, 1196, 1116.

UV spectrum (EtOH, λ_{max}, nm, log ε): 212 (4.77), 252 (4.06), 262 (4.08), 326 (4.29).

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.36, 1.41 (6H, two s, two CH_3-2), 1.63 (4H, m, CH_2-8, CH_2-9), 1.87 (1H, dd, J = 12.0, J = 5.7, H-3α), 1.99 (1H, dd, J = 12.0, J = 2.4, H-3β), 2.37 (2H, m, CH_2-10), 2.95 (2H, m, CH_2-7), 3.79 (1H, s, CH_3O-11), 4.92 (1H, m, H-4), 5.05 (1H, d, J = 5.4, OH-4), 6.31 (1H, s, H-12).

11-Methoxy-2,2-dimethyl-7,8,9,10-tetrahydrobenzo[*c*]pyrano[2,3-*h*]chromen-6-one (21). A solution of **20** (1.00 g, 3 mmol) in dioxane (10 mL) was treated with HCl solution (4 M, 10 mL). The reaction mixture was held at room temperature and vigorously stirred for 4 h (completion of reaction was determined using TLC). After the reaction was complete, solvent was removed in vacuo in a rotary evaporator. The solid was crystallized from MeOH, yield 79%, mp 236-237°C, $C_{19}H_{20}O_4$. IR spectrum (KBr, cm^{-1}): 1708, 1620, 1580, 1484, 1366, 1140, 1118, 1106.

UV spectrum (EtOH, λ_{max}, nm, log ε): 230 (4.63), 292 (4.33), 326 (4.24).

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.40 (6H, s, two CH_3-2), 1.62 (4H, m, CH_2-8, CH_2-9), 2.34 (2H, m, CH_2-10), 2.90 (2H, m, CH_2-7), 3.79 (3H, s, CH_3O-11), 5.70 (1H, d, J = 9.6, H-3), 6.37 (1H, s, H-12), 6.61 (1H, d, J = 9.6, H-4).

Hexahydrobenzo[*c*]pyrano[2,3-*h*]chromen-6-ones 23 and 24. A solution of **20** (3.12 g, 15 mmol) and ethyl-2-oxocyclohexanecarboxylate (2.40 mL, 15 mmol) in EtOH (10 mL) was stirred vigorously and treated dropwise with conc. H_2SO_4

(20 mL). The resulting mixture was held at 50°C for 4 h, left overnight at room temperature, and poured into icewater (100 mL). The resulting precipitate was dissolved in $CHCl_3$ (50 mL) and treated with NaOH solution (1 N, 2×50 mL) and saturated NaCl solution. The organic phase was dried over anhydrous $MgSO_4$. Solvent was removed in vacuo in a rotary evaporator. The oily residue was crystallized from MeOH to afford **23**. The combined alkaline solutions were acidified to pH 4. The resulting precipitate of **24** was filtered off and crystallized from propan-2-ol.

11-Methoxy-2,2-dimethyl-3,4,7,8,9,10-hexahydrobenzo[*c*]pyrano[2,3-*h*]chromen-6-one (23), yield 39%, mp 175-176°C, $C_{19}H_{22}O_4$. IR spectrum (KBr, cm^{-1}): 1714, 1622, 1602, 1486, 1470, 1436, 1378, 1326, 1208, 1152, 1122, 1082.

UV spectrum (CH_3CN, λ_{max}, nm, log ε): 209 (4.51), 253 (3.94), 262 (3.92), 333 (4.12).

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.31 (6H, s, two CH_3-2), 1.66 (4H, m, CH_2-8, CH_2-9), 1.80 (2H, t, J = 7.2, CH_2-3), 2.36 (2H, m, CH_2-10), 2.68 (2H, t, J = 7.2, CH_2-4), 2.96 (2H, m, CH_2-7), 3.78 (3H, s, CH_3O-11), 6.24 (1H, s, H-12).

11-Hydroxy-2,2-dimethyl-3,4,7,8,9,10-hexahydrobenzo[*c*]pyrano[2,3-*h*]chromen-6-one (24), yield 45%, mp 188-189°C, $C_{18}H_{20}O_4$. IR spectrum (KBr, cm^{-1}): 3296, 2972, 1690, 1666, 1612, 1566, 1428, 1396, 1368, 1284, 1260, 1156, 1076.

UV spectrum (EtOH, λ_{max}, nm, log ε): 213 (4.65), 251 (3.93), 260 (3.94), 329 (4.31).

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.33 (6H, s, two CH_3-2), 1.67 (4H, m, CH_2-8, CH_2-9), 1.74 (2H, t, J = 7.2, CH_2-3), 2.35 (2H, m, CH_2-10), 2.64 (2H, t, J = 7.2, CH_2-4), 3.02 (2H, m, CH_2-7), 6.25 (1H, s, H-12), 10.13 (1H, s, OH-11).

2,2-Dimethyl-11-(2-oxopropoxy)-3,4,7,8,9,10-hexahydrobenzo[*c*]pyrano[2,3-*h*]chromen-6-one (25). A hot solution of **24** (1.20 g, 4 mmol) in absolute acetone (20 mL) was treated with freshly calcined potash (1.66 g, 10 mmol), stirred vigorously, heated (50-56°C), and treated with chloroacetone (0.35 mL, 4.4 mmol). The resulting mixture was heated for 3 h and stirred vigorously (course of reaction was monitored using TLC). After the reaction was complete, the mixture was cooled to room temperature, poured into icewater (100 mL), and acidified to pH 4. The solid was filtered off and crystallized from propan-2-ol (75%), yield 85%, mp 174-175°C, $C_{21}H_{24}O_5$. IR spectrum (KBr, cm^{-1}): 1728, 1710, 1610, 1432, 1392, 1292, 1160, 1132.

UV spectrum (EtOH, λ_{max}, nm, log ε): 214 (4.74), 321 (4.42).

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.35 (6H, s, two CH_3-2), 1.68 (2H, m, CH_2-8, CH_2-9), 1.78 (2H, t, J = 7.2, CH_2-3), 2.19 (3H, s, CH_3-3′), 2.37 (2H, m, CH_2-10), 2.66 (2H, t, J = 7.2, CH_2-4), 3.04 (2H, m, CH_2-7), 4.84 (2H, s, CH_2-1′), 6.39 (1H, s, H-12).

3,5,5-Trimethyl-6,7,10,11,12,13-hexahydrobenzo[*c*]furo[2,3-*f*]pyrano[2,3-*h*]chromen-9-one (26). A solution of **25** (1.07 g, 3 mmol) in propan-2-ol (10 mL) was treated with NaOH solution (1 N, 10 mL). The reaction mixture was heated for 3 h (completion of reaction was determined using TLC). After the reaction was complete, the mixture was cooled to room temperature, poured into icewater (100 mL), and acidified to pH 4. The solid was filtered off and crystallized from propan-2-ol (75%), yield 91%, mp 232-233°C, $C_{21}H_{22}O_4$. IR spectrum (KBr, cm^{-1}): 1702, 1680, 1616, 1582, 1468, 1420, 1370, 1312, 1280, 1266, 1156, 1126.

UV spectrum (EtOH, λ_{max}, nm, log ε): 210 (4.48), 230 (4.39), 259 (4.33), 274 (4.30), 313 (4.17).

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.38 (6H, s, two CH_3-5), 1.71 (4H, m, CH_2-11, CH_2-12), 1.84 (2H, t, J = 6.6, CH_2-6), 2.38 (3H, s, CH_3-3), 2.43 (2H, m, CH_2-13), 2.86 (2H, t, J = 6.6, CH_2-7), 3.08 (2H, m, CH_2-10), 7.52 (1H, s, H-2).

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