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# Facile synthesis of polyhydroxycoumaronochromones with quinones: synthesis of alkylpolyhydroxy- and alkoxycoumaronochromones from 2′-hydroxyisoflavones

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**Abstract**—4′,5,7-Trihydroxy- or 8-alkyl-4′,5,7-trihydroxycoumaronochromones were synthesized by oxidative cyclization of the corresponding 2′-hydroxyisoflavones with *o*-chloranil under mild conditions. By contrast, alkoxycoumaronochromones were synthesized by oxidative cyclization of the corresponding 2′-hydroxyisoflavones with DDQ. 

Coumaronochromones (=benzofuro[2,3-*b*][1]benzopyran-11-ones) occur along with isoflavones in nature, and lisetin was known as the single example of these compounds for many years, although, recently, the structures of many coumaronochromones have been characterized by spectroscopic studies.[1] Lisetin [4′,5,7-trihydroxy-5′-methoxy-3′-(3-methyl-2-butenyl)coumaronochromone] was synthesized by oxidative cyclization of piscerythrone (2′-hydroxyisoflavone) with $K_3[Fe(CN)_6]$ in low yield,[1b] and other unsubstituted or *O*-alkylated coumaronochromones, albeit in generally low yields, were synthesized by oxidation of the corresponding 2′-hydroxyisoflavones with oxidants such as $Ag_2CO_3$, lead(IV) acetate, and $SeO_2$.[2] Recently, new and unique alkyl- or alkenylpolyhydroxycoumaronochromones such as lupiltin, lupinalubin B, etc. have been isolated as a small amount of the components along with several new isoflavones from the roots of white lupin (*Lupinus albus* L.) and the structures have been identified by spectroscopic studies.[3] The total synthesis of these coumaronochromones has not been achieved yet, although a biosynthetic pathway of coumaronochromones from isoflavone precursors has been proposed by Ollis and his colleagues.[4] The reason seems to be due to difficulty in introducing regioselectively an alkyl or alkenyl group into the isoflavone or coumaronochromone nucleus and the selectivity of protection and deprotection of the hydroxy groups in the molecule. For the synthesis of coumaronochromones, it is also necessary to investigate the suitable oxidants for the biogenetic-like dehydrocyclization of 2′-hydroxyisoflavones. Quinones have been applied occasionally as dehydrogenating reagents under mild conditions; high-potential quinones such as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) or tetrachloro-1,2-benzoquinone (*o*-chloranil) reacted with hydroaromatic compounds, benzylic alcohols, and *o*-(3,3-dialkylallyl)phenols under mild conditions to give the corresponding dehydrogenated aromatic compounds, carbonyl compounds, and chromenes in good yields, respectively.[1a,5] Our interest in high dehydrogenation of the phenol compounds by the quinones under mild conditions encouraged us to apply this methodology to the preparation of *C*-alkyl- or *C*-alkenylpolyhydroxycoumaronochromones from the corresponding 2′-hydroxyisoflavones.

We have examined for the first time the simple and general applicability of DDQ or *o*-chloranil to the synthesis of polyhydroxycoumaronochromones from the corresponding 2′-hydroxyisoflavones and report here on the first syntheses of lupilutin (1,3,8-trihydroxy-4-(3-hydroxy-3-methylbutyl)benzofuro[2,3-*b*][1]benzopyran-11-one) (**1**),[6] 4′,5,7-trihydroxy-4-(3-methyl-2-butenyl)benzofuro[2,3-*b*][1]benzopyran-11-one) (**2**), lupinalbin A (4′,5,7-trihydroxycoumaronochromone) (**3**),[3] and 4′,5,7-trihydroxy-5′-methoxycoumaronochromone (**4**), alkoxycoumaronochromones **5**[1b] and **6**. Compounds **2**, **4**, **5** and **6** have yet to be isolated from natural sources.

*Keywords*: coumaronochromones; 2′-hydroxyisoflavones; oxidative cyclization; *o*-chloranil.

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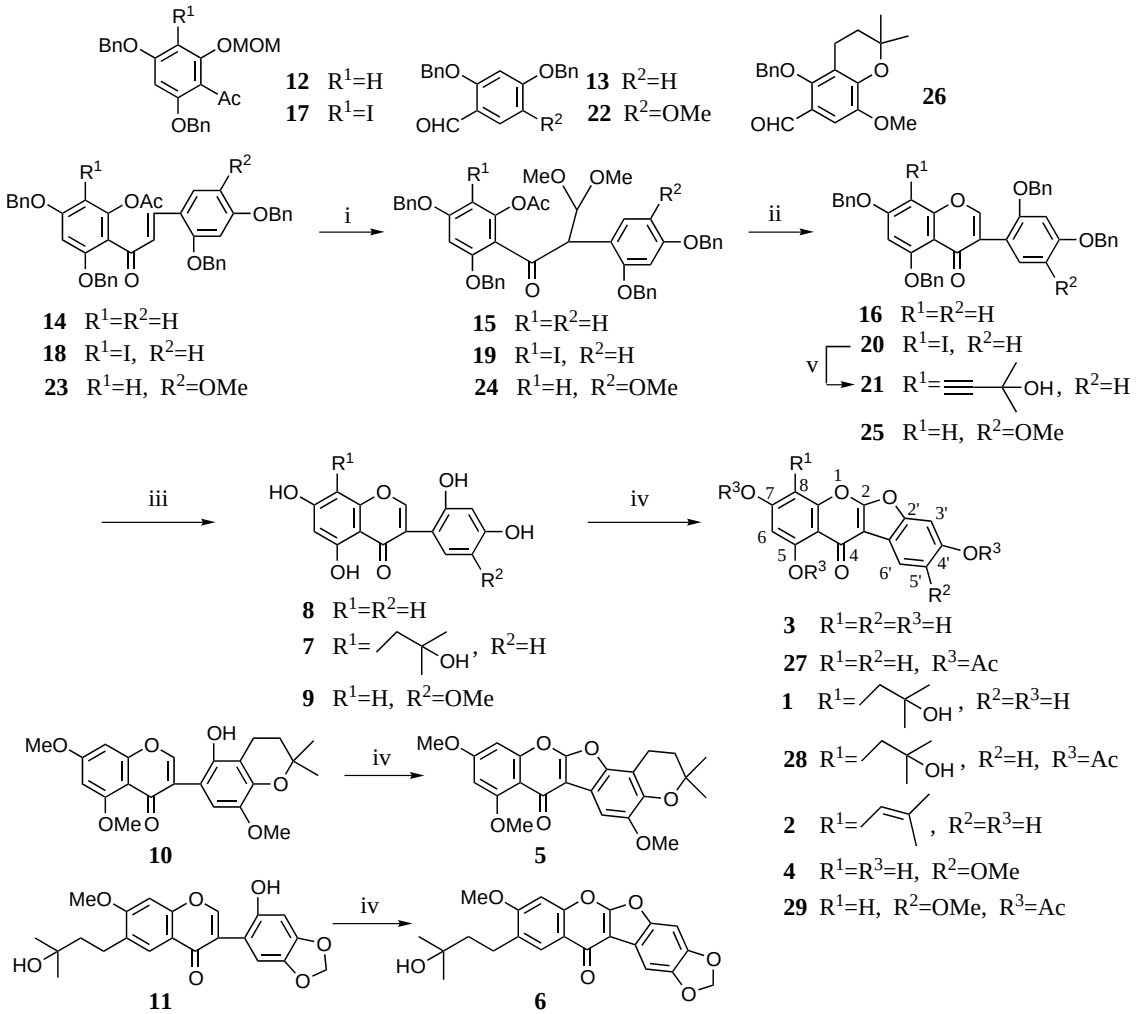
Condensation of 2′-(methoxymethoxy)acetophenone **12**[7] with benzaldehyde **13** in the presence the of KOH at 85°C in ethanol gave the corresponding 2′-(methoxymethoxy)chalcone, which was converted into 2′-acetoxychalcone **14** (mp 115–116°C, 68% overall) by demethoxymethylation with hydrochloric acid and the subsequent acetylation of the resulting 2′-hydroxychalcone by the acetic anhydride/pyridine method (Scheme 1). Oxidative rearrangement of **14** with thallium(III) nitrate trihydrate (TTN), followed by cyclization of the resulting crude acetal **15** with aqueous NaOH gave isoflavone **16** (mp 178–179°C), which was converted into tetrahydroxyisoflavone **8**[8] (mp 254–256°C) by catalytic hydrogenation over Pd/C.[7] 8-Iodoisoflavone **20** (mp 151–152°C) also was synthesized via condensation of 3′-iodoacetophenone **17**[7] with **13**, followed by oxidative rearrangement of the resulting 3′-iodochalcone **18** (mp 82–83°C, 72% overall) and the subsequent cyclization of acetal **19** by the same procedure as that used to prepare **16**. Coupling reaction of **20** with 2-methyl-3-butyn-2-ol in the presence of Pd(0)[9] gave easily the 8-(3-hydroxy-3-methylbutynyl)isoflavone **21** (mp 221–223°C), which was hydrogenated over Pd/C to give 8-(3-hydroxy-3-methylbutyl)isoflavone **7**.[6,7] Oxidative rearrangement of 5′-benzyloxy-2′-methoxyacetophenone with a mixture of *m*-chloroperbenzoic acid and trifluoroacetic acid in dichloromethane at 0°C to room temperature, followed by hydrolysis of the resulting crude acetate with 10% aqueous NaOH in methanol/dioxane gave 5-benzyloxy-2-methoxyphenol (mp 106–108°C, 72% overall), which was converted into 2,4-bis(benzyloxy)-1-methoxybenzene (95%) by using benzyl chloride and $K_2CO_3$ in DMF at 80°C. Formylation of the 1-methoxybenzene with DMF–phosphoryl chloride in 1,2-dichloroethane gave 5-methoxybenzaldehyde **22**.[10] The condensation of **12** with **22** gave chalcone **23** (mp 111–112°C, 76% overall), which was converted into tetrahydroxy-5′-methoxyisoflavone **9** (mp 267°C, decomposition) via acetal **24** and the subsequent isoflavone **25** (mp 152–154°C) by the same procedure as that used to prepare **8**. The reaction of 2,4-dihydroxy-5-methoxybenzaldehyde, prepared from




**Scheme 1.** *Reagents and conditions*: (i) $CHCl_3$/MeOH, TTN (2 equiv.), 40°C, 2 h, each crude solid; (ii) THF/MeOH, 10% NaOH, 35°C, 2 h, 75–80% from (i); (iii) 1,4-dioxane/MeOH, $H_2$, 5% Pd/C, rt, 8 h, 81–92%; (iv) 1,4-dioxane, DDQ or *o*-chloranil; (v) 2-methyl-3-butyn-2-ol, $PdCl_2$ (3 mol%), $PPh_3$ (6 mol%), CuI (3 mol%), $NEt_3$/DMF, 85°C, 2 h, 77%.

**Table 1.** Oxidative cyclization of 2′-hydroxyisoflavones to coumaronochromones by DDQ or *o*-chloranil

| Isoflavone | Quinone (equiv.) | Solvent | Temp. (°C) | Time (h) | Product (yield %)[a] |
|---|---|---|---|---|---|
| **7** | DDQ (2.2) | THF | 50 | 0.5 | Decomposed |
| | *o*-Chloranil (2.3) | Dioxane | 80 | 2 | **1** (71) |
| | | | | | **2** (73)[b] |
| **8** | DDQ (2.2) | THF | 50 | 0.5 | **3** (63) |
| | *o*-Chloranil (2.3) | Dioxane | 80 | 2 | **3** (50)[c] |
| **9** | DDQ (1.2) | Dioxane | 25 | 0.5 | Decomposed |
| | *o*-chloranil (2.3) | Dioxane | 80 | 2 | **4** (49) |
| **10** | DDQ (1.2) | THF | 25 | 2 | **5** (78) |
| **11** | DDQ (1.2) | THF | 25 | 2 | **6** (82) |

[a] Isolated yields.
[b] Overall yield from **28** via dehydration and hydrolysis.
[c] Overall yield from **8** via **27**.

**22** in 94% yield by debenzylation, with 2-methyl-3-buten-2-ol in the presence of $BF_3{\cdot}OEt_2$ in dioxane gave 2,4-dihydroxy-5-methoxy-3-(3-methyl-2-butenyl)benzaldehyde (40%), whose cyclization with HCl, followed by benzylation of the resulting crude 6-formyl-5-hydroxy-8-methoxy-2,2-dimethylchroman, afforded 5-benzyloxy-2,2-dimethylchroman **26** (mp 164–165°C, overall 20%). Condensation of 4′,6′-dimethoxy-2′-methoxymethoxyacetophenone with **26** gave 2′-hydroxydihydropyranoisoflavone **10** (mp 235–237°C, 27% overall) by the same procedure as that used to prepare **8**.

To a THF solution of 2′-hydroxyisoflavone **8**, DDQ (1.2 equiv.) was added under mild conditions and stirred for 10 min, and subsequently DDQ (1.0 equiv.) was again added into the solution, and the reaction was completed in 30 min. The reaction mixture was purified by silica-gel column chromatography to give the desired coumaronochromone **3**[11] in good yield as shown in Table 1. Oxidative cyclization of **8** with *o*-chloranil [the reduction potential (0.83 V) is lower than that (1.0 V) of DDQ][5] in dioxane at 80°C, followed by acetylation of the resulting crude compound **3**[11] gave triacetate **27**[3] (mp 256–258°C, 55%), which was hydrolyzed to **3**. Oxidation of 8-alkylisoflavone **7** with DDQ or $K_3[Fe(CN)_6]$ led to decomposition and the desired coumaronochromone **1** was not obtained. Oxidative decomposition of compound **7** with DDQ would take place via the formation of a 5,8-quinomethide structure. Oxidative cyclization of **7** with *o*-chloranil gave easily the desired compound **1**,[11] which was converted into triacetate **28** (mp 202–204°C). Dehydration of **28** with $BF_3{\cdot}OEt_2$ in $CH_2Cl_2$ at 20°C, followed by hydrolysis of the resulting crude 8-prenylcoumaronochromone gave easily trihydroxy-8-prenylcoumaronochromone **2**.[11] Oxidation of 5′-methoxyisoflavone **9** with DDQ also led to decomposition and the desired coumaronochromone **4** was not obtained, because oxidative decomposition would probably proceed via the 4′,5′-quinoid formation. Oxidative cyclization of **9** with *o*-chloranil, however, gave compound **4**,[11] which was converted into triacetate **29** (mp 250–252°C). Oxidative cyclization of alkoxyisoflavone **10** and 6-alkylisoflavone **11**[12] with DDQ gave the corresponding coumaronochromones **5**[11] and **6**[11] in high yields, respectively. Because alkoxyisoflavones **10** and **11** do not contain free hydroxy groups, which are highly susceptible to oxidation with DDQ, the oxidation of these compounds would not lead to decomposition.

On the basis of the above results, the oxidative cyclization of alkoxy-2′-hydroxyisoflavones with DDQ gave the desired coumaronochromones in high yields, while alkylpolyhydroxyisoflavones were shown to be easily oxidized to the corresponding coumaronochromones by *o*-chloranil.

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10. Compound **22**: Colorless needles; mp 112–114°C (94%); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.88 (3H, s, $OCH_3$), 5.04 and 5.18 (each 2H, s, $OCH_2$), 6.55 (1H, s, 3-H), 7.34–7.39 (11H, m, Ar-H), 10.35 (1H, s, CHO). Found: C, 75.92; H, 5.91; calcd for $C_{22}H_{20}O_4$: C, 75.84; H, 5.79%.

11. Compound **3**: Colorless needles; mp >300°C; $^1$H NMR (400 MHz, $(CD_3)_2CO$): $\delta$ 6.37 (1H, d, $J=2.4$ Hz, 6-H), 6.60 (1H, d, $J=2.4$ Hz, 8-H), 7.02 (1H, dd, $J=2.0$ and 8.3 Hz, 5′-H), 7.14 (1H, d, $J=2.0$ Hz, 3′-H), 7.81 (1H, d, $J=8.3$ Hz, 6′-H), 8.90 and 9.77 (each 1H, s, OH), 12.99 (1H, s, 5-OH). Found: C, 61.72; H, 3.31; calcd for $C_{15}H_8O_6\cdot 1/2H_2O$: C, 61.44; H, 3.10%. Compound **1**: Colorless needles; mp 286–288°C (lit. [7] 284–286°C); $^1$H NMR (400 MHz, $(CD_3)_2CO$): $\delta$ 1.31 (6H, s, $CH_3\times 2$), 1.78 (2H, m, 2″-H), 2.92 (2H, m, 1″-H), 3.65 (1H, br s, 3″-OH), 6.43 (1H, s, 6-H), 7.01 (1H, dd, $J=8.3$ and 2.0 Hz, 5′-H), 7.14 (1H, d, $J=2.0$ Hz, 3′-H), 7.80 (1H, d, $J=8.3$ Hz, 6′-H), 8.99 and 9.98 (each 1H, br s, OH), 12.93 (1H, s, 5-OH). IR (KBr): 3450, 1650, 1600, 1500, 1420, 1320, 1210, 1130, 1100 cm$^{-1}$. Found: C, 64.94; H, 4.96; calcd for $C_{20}H_{18}O_7$: C, 64.86; H, 4.90%. Compound **2**: Colorless needles; mp 259–261°C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.67 and 1.87 (each 3H, s, $CH_3$), 3.51 (2H, d, $J=7.3$ Hz, 1″-H), 5.28 (1H, t, $J=7.3$ Hz, 2″-H), 6.44 (1H, s, 6-H), 7.02 (1H, dd, $J=8.3$ and 2.0 Hz, 5′-H), 7.15 (1H, d, $J=2.0$ Hz, 3′-H), 7.81 (1H, d, $J=8.3$ Hz, 6′-H), 8.88 and 9.75 (each 1H, br s, OH), 12.94 (1H, s, 5-OH). $m/z$ (EI): 352 ($M^+$, 100). Found: C, 64.80; H, 4.82; calcd for $C_{20}H_{16}O_6\cdot H_2O$: C, 64.86; H, 4.90%. Compound **4**: Colorless needles; mp>300°C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 3.87 (3H, s, $OCH_3$), 6.30 (1H, s, 6-H), 6.56 (1H, s, 8-H), 7.18 (1H, s, 3′-H), 7.36 (1H, s, 6′-H), 9.53 (1H, s, OH), 10.94 (1H, br s, OH), 12.91 (1H, s, 5-OH). Found: C, 61.15; H, 3.21; calcd for $C_{16}H_{10}O_7$: C, 60.95; H, 3.48%. Compound **5**: Colorless needles; mp 277–279°C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.44 (6H, s, $CH_3\times 2$), 1.90 (2H, t, $J=6.8$ Hz, 2″-H), 2.98 (2H, t, $J=6.8$ Hz, 1″-H), 3.91, 3.93 and 3.98 (each 3H, s, $OCH_3$), 6.46 (1H, d, $J=2.4$ Hz, 6-H), 6.60 (1H, d, $J=2.4$ Hz, 8-H), 7.52 (1H, s, 6′-H). Found: C, 67.07; H, 5.39; calcd for $C_{23}H_{22}O_7$: C, 67.31; H, 5.40%. Compound **6**: Colorless needles; mp 237–239°C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.32 (6H, s, $CH_3\times 2$), 1.82 (2H, m, 2″-H), 2.81 (2H, m, 1″-H), 3.97 (3H, s, $OCH_3$), 6.05 (2H, s, $OCH_2O$), 6.96, 7.05, 7.26 and 8.11 (each 1H, s, Ar-H). Found: C, 66.55; H, 5.65; calcd for $C_{22}H_{22}O_7$: C, 66.34; H, 5.57%.

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