Regioselective Synthesis of 6-Alkyl- and 6-Prenylpolyhydroxyisoflavones and 6-Alkylcoumaronochromone Derivatives

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The palladium-catalyzed coupling reaction of 6-iodoisoflavone, prepared from 3′-iodoacetophenone derivative, with 2-methyl-3-butyn-2-ol gave 6-alkynylisoflavone derivative, which was hydrogenated to give 6-alkylhydroxyisoflavone (luteone hydrate) (2). Dehydration of 2 gave 2′,4′,5,7-tetrahydroxy-6-prenylisoflavone (luteone) (1). Wighteone hydrate (3) was also synthesized from 6-iodotris(benzyloxy)isoflavone in a similar manner. 6-Alkyl-4′5,7-trihydroxy-coumaronochromone (4) was synthesized by oxidative cyclization of 2 with *o*-chloranil.

Key words iodoisoflavone; prenylisoflavone; luteone; regioselective prenylation; coumaronochromone; *o*-chloranil

Prenyl (=3-methyl-2-butenyl)isoflavones and (3-hydroxy-3-methylbutyl)isoflavones, which contain an alkyl or alkenyl group in the A- and/or B-ring, are widely distributed in nature and have antifungal activity.[1—4] Luteone, known as a phytoalexin, was first isolated in 1973 from immature fruits of *Lupinus luteus* (*Leguminosae*).[5] The structure was assigned as 2′,4′,5,7-tetrahydroxy-6-(3-methyl-2-butenyl)isoflavone (**1**) by spectroscopic and chemical studies. The same isoflavone **1** was also isolated from healthy leaves or roots of white lupin (*Lupinus albus L.*, cv Kievskij Mutant)[4,6] and the roots of yellow lupin (*Lupinus leuteus L.*, cv. Barpin) together with luteone hydrate, the structure of which was assigned to be 2′,4′,5,7-tetrahydroxy-6-(3-hydroxy-3-methylbutyl)isoflavone (**2**) by spectroscopic analysis.[7] Luteone hydrate (**2**) was isolated as a fungal metabolite of luteone (**1**) with cultures of *Aspergillus flavus* and *Botrytis cinerea*.[8] Wighteone hydrate [4′,5,7-trihydroxy-6-(3-hydroxy-3-methylbutyl)isoflavone] (**3**) was also isolated as a fungal metabolite of wighteone [4′,5,7-trihydroxy-6-(3-methyl-2-butenyl)isoflavone][2,6,7,9] with cultures of *A. flavus* and *B. cinerea*.[10] In view of the isolation of **1** and **2** from the same natural source, it is considered that **2** is a precursor of **1** and dehydration of **2** would lead to **1**. The total syntheses of isoflavones **1**, **2**, and **3** have not been achieved yet, although the dimethyl ether of luteone (**1**) has been synthesized.[11] The reason seems to be due to the difficulty in introducing an alkyl or alkenyl group regioselectively into the isoflavone nucleus and the selectivity of protection and consequent deprotection. Furthermore, 6-alkylpolyhydroxyisoflavones are isomerized to the corresponding isomers, 8-alkylpolyhydroxyisoflavones, by bases.[12,13] We need to solve these problems for the regioselective synthesis of these phloroglucin-type 6-prenylisoflavones. In our previous paper,[14] we reported the regioselective synthesis of prenylisoflavones. As a continuation of our studies on the regioselective synthesis of alkyl- and prenylisoflavones, we wish to report here on the first syntheses of **1**, **2**, and **3** using the palladium (0)-catalyzed coupling reaction[15] of the corresponding iodoisoflavone with 2-methyl-3-butyn-2-ol.[16] Recently, the new coumaronochromones (=benzofuro[2,3-*b*][1]benzopyran-11-ones) lupilutin (8-alkylcoumaronochromone from the root of yellow lupin)[7] and lupinalbin B (6-prenylcoumaronochromone from the root of white lupin)[17] have also been isolated. However, 6-alkylcoumaronochromone (**4**), which is considered to be a precursor of lupinalbin B, has yet to be isolated from natural sources. We have examined the simple and general applicability of DDQ or *o*-chloranil to the synthesis of alkylpolyhydroxycoumaronochromones from the corresponding 2′-hydroxyisoflavones.[18] We wish to report here the synthesis of compound **4** by oxidative cyclization of compound **2** with *o*-chloranil.

Results and Discussion

The catalytic hydrogenation of 2′,4′-bis(benzyloxy)-6′-methoxymethoxyacetophenone[14] over Pd/C, followed by iodination of the resulting 2′,4′-dihydroxyacetophenone **5** with I_2 and H_5IO_6[19] gave the 3′-iodoacetophenone **6** in 92% yield. Compound **6** was converted into bis(benzyloxy)acetophenone **7**, the structure of which was determined by direct comparison with a sample of the isomer [2′,4′-bis(benzyloxy)-5′-iodo-6′-methoxymethoxyacetophenone (mp 99—100 °C)[14]] and ^{1}H-NMR-NOE analysis. The mixture of **7** with the isomer showed a marked decrease in the melting point relative to that of each compound. Compound **7** was not obtainable by the I_2-CF_3CO_2Ag method.[14] Condensation of **7** with 2,4-bis(benzyloxy)benzaldehyde in the presence of sodium hydroxide gave 6′-methoxymethoxychalcone **8**, and then the methoxymethyl group in the chalcone was cleaved by treatment with dilute HCl to give 3′-iodo-6′-hydroxychalcone **9** in 86% yield. Oxidative rearrangement of acetate **10**, prepared from **9**, with thallium(III) nitrate trihydrate (TTN),[20] followed by hydrolysis of the resulting mixture **11** with aqueous sodium hydroxide gave the desired 6-iodoisoflavone **12** in 40% yield and the chalcone **9**, the structures of which were identified by ^{1}H-NMR spectral analysis. On the basis of the results, it was shown that deacetylation of **10** with TTN took place more easily than the oxidative rearrangement of the phenyl group of **10** to give the chalcone **9**. Therefore **9** was converted into benzoate **13**, which was oxidatively rearranged with TTN to give the corresponding acetal **14** easily. The crude acetal **14** was hydrolyzed with aqueous sodium hydroxide to give the 6-iodoisoflavone **12** in 70% yield *via* two steps from **13**. The coupling reaction of **12** with 2-methyl-3-butyn-2-ol in the presence of Pd(0) in triethylamine gave 6-(3-hydroxy-3-methylbutynyl)isoflavone **15** in 71% yield. The catalytic hydrogenation of **15** gave 2′,4′,5,7-

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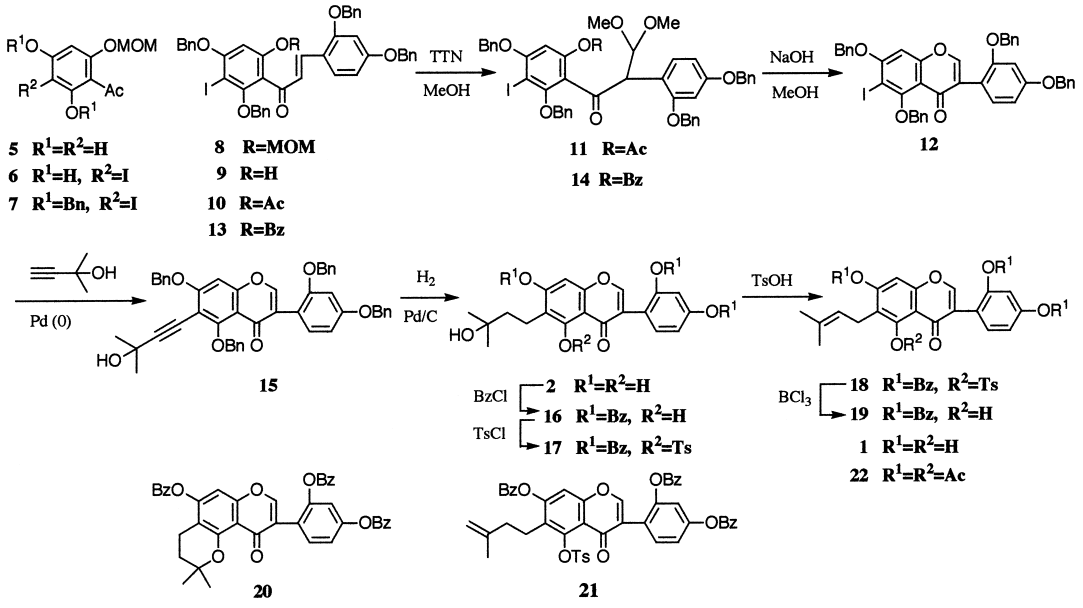

Chart 1

Table 1. ^{1}H-NMR (400 MHz, CD_3COCD_3) Data for Prenyl- and Alkylisoflavones **1**, **2**, Luteone, and Luteone Hydrate[a)]

Compound	2-H	8-H	3′-H	5′-H	6′-H 2′-H	Me	CH_2	CH=C	OH
1	8.14 s	6.53 s	6.48 d (*J*=2.4)	6.44 dd (*J*=2.4, 8.3)	7.12 d (*J*=8.3)	1.65 s 1.78 s	3.37 d (*J*=7.3)	5.28 t (*J*=7.3)	8.31 br s, 8.43 br s 9.23 br s, 13.06 s
Natural product[7)] (**1**)	8.14 s	6.53 s	6.48 d (Incomplete)	6.43 dd (*J*=2.4, 8.9)	7.12 d (*J*=8.9)	1.65 s 1.78 s	3.37 br d (*J*=7.3)	5.28 br t (*J*=7)	13.05 s
2	8.15 s	6.52 s	6.49 d (*J*=2.4)	6.44 dd (*J*=2.4, 8.3)	7.12 d (*J*=8.3)	1.26 s (6H)	1.71 m 2.79 m		3.59 br s 8.32 s, 8.43 s 9.29 br s, 13.05 s
Natural product[7)] (**2**)	8.14 s	6.51 s	6.48 d (Incomplete)	6.43 dd (*J*=2.4, 8.8)	7.12 d (*J*=8.8)	1.25 s (6H)	1.71 m 2.81 m		13.04 s
3	8.15 s	6.47 s	6.90 d (*J*=8.8)	6.90 d (*J*=8.8)	7.45 d (*J*=8.8) 7.45 d (*J*=8.8)	1.26 s (6H)	1.71 m 2.78 m		8.50 br s, 9.65 br s 13.33 s

a) s, singlet; d, doublet; dd, double doublet; t, triplet; br, broad; m, multiplet.

tetrahydroxy-6-(3-hydroxy-3-methylbutyl)isoflavone (**2**) in 96% yield. The ^{1}H-NMR spectrum of **2** was identical to that of a natural sample of luteone hydrate[7)] (Table 1) and other physical properties (see Experimental). On the basis of these results, the structure of luteone hydrate was confirmed by the first synthesis of 2′,4′,5,7-tetrahydroxy-6-(3-hydroxy-3-methylbutyl)isoflavone (**2**).

Exhaustive benzoylation (7 h) of **2** afforded partly the isomer [2′,4′,7-tris(benzoyloxy)-5-hydroxy-8-(3-hydroxy-3-methylbutyl)isoflavone]. To prevent the isomerization, the partial benzoylation of compound **2** gave 2′,4′,7-tris(benzoyloxy)isoflavone **16** for 30 min in 85% yield, and subsequently compound **16** was tosylated for 20 min to give 5-tosyloxyisoflavone **17** in 91% yield. Compound **17** was dehydrated with $BF_3 \cdot OEt_2$ at room temperature to give 6-prenyl-5-tosyloxyisoflavone **18** (20%), 5-hydroxy-6-prenylisoflavone **19** (25%), and dihydropyran derivative **20** (45%), respectively. In this reaction, it was shown that part of **18** was initially detosylated, and the resulting compound **19** was subsequently cyclized to give **20**. The formation of **20** strongly supported the structure of **2** and decreased the yield of **19**. The tosylate **17** was dehydrated with $TsOH \cdot H_2O$ to give a mixture of 6-prenylisoflavone **18** and the regioisomer 6-(3-methyl-3-butenyl)isoflavone **21**. The ^{1}H-NMR spectrum of the tosylate mixture (**18** and **21**) showed the ratio of **18** to **21** to be 85 : 15 [peaks due to $C\underline{H}_2CH=C(CH_3)_2$ at δ=3.36 (2H, d) and $CH_2CH_2C(CH_3)=C\underline{H}_2$ at δ=4.57 (2H, s)]. The mixture (**18** and **21**) reacted quantitatively with benzohydroximoyl chloride[14)] in dry CH_2Cl_2 at room temperature to give a mixture of the unchanged 6-prenylisoflavone **18** and the terminal alkene-cyclic adduct, and then **18** was purified by silica gel column chromatography. The detosylation of **18** with BCl_3, followed by hydrolysis of the resultant compound **19** with 10% NaOH in a mixture of methanol and dioxane at room temperature, gave 2′,4′,5,7-tetrahydroxy-6-(3-methyl-2-butenyl)isoflavone (**1**) in 66% yield (^{1}H-NMR in Table 1), which was converted into the tetraacetate derivative **22**. The ^{1}H-NMR, IR, and UV spectral data for **1** were completely identical to those of a natural sample of luteone.[5,6)] On the basis of these results, the structure of luteone was confirmed for the first time by the synthesis of 2′,4′,5,7-tetrahydroxy-6-(3-methyl-2-butenyl)isoflavone (**1**).

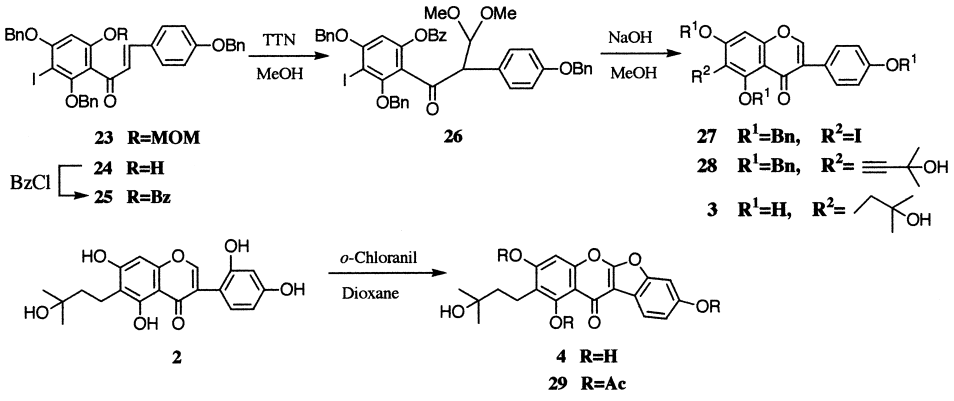

Chart 2

Condensation of **7** with 4-benzyloxybenzaldehyde and the subsequent hydrolysis of the resultant chalcone **23** gave 6′-hydroxychalcone **24**, which was converted into the corresponding benzoate **25**. The oxidative rearrangement of **25** with TTN for 20 h, followed by the hydrolysis of the resultant acetal **26**, gave the corresponding 4′-benzyloxy-6-iodoisoflavone **27** in 30% yield *via* three steps from **24**. The yield of compound **27** was lower than that of the 2′,4′-bis(benzyloxy)-6-iodoisoflavone **12**. The reason depends on the number of the electron-releasing subtituents in the B-ring.[12,21] The coupling reaction of **27** with 2-methyl-3-butyn-2-ol in the presence of Pd(0) gave 6-(3-hydroxy-3-methyl-1-butynyl)isoflavone **28** in 57% yield. The catalytic hydrogenation of **28** over Pd/C gave 4′,5,7-trihydroxy-6-(3-hydroxy-3-methylbutyl)isoflavone (**3**) in 92% yield. The ^{1}H-NMR spectrum and other physical properties were identical to those of a natural sample of wighteone hydrate[10] (Table 1). On the basis of these results, the structure of wighteone hydrate was confirmed by the synthesis of 4′,5,7-trihydroxy-6-(3-hydroxy-3-methylbutyl)isoflavone (**3**).

The oxidative cyclization of the 2′-hydroxyisoflavone **2** with *o*-chloranil (2.2 eq) [the reduction potential (0.83 V) is lower than that (1.0 V) of DDQ][22,23] in dioxane gave the desired coumaronochromone **4** at 80 °C for 2 h in good yield. Compound **4** was easily converted into diacetate **29** at 0 °C using the acetic anhydride-pyridine method.

The present regioselective synthesis of iodoisoflavones and the palladium (0)-catalyzed coupling reaction of iodoisoflavones with 2-methyl-3-butyn-2-ol have been shown to be efficient and useful procedures for the syntheses of prenyl- and alkylpolyhydroxyisoflavones and *O*-alkylated prenylisoflavones.

Experimental

All the melting points were measured on a Yanaco MP-J3 micro melting-point apparatus and are uncorrected. The ^{1}H-NMR spectra were measured with a JEOL EX400 spectrometer (400 MHz), using tetramethylsilane as internal standard (δ, ppm). The IR spectra were recorded on a Hitachi 215 spectrophotometer, and the UV spectra were recorded on a Hitachi 124 spectrophotometer. Elemental analyses were performed with a Yanaco CHN corder model MT-5. Column chromatography and thin-layer chromatography (TLC) were carried out on Kieselgel 60 (70—230 mesh) and Kieselgel 60 F-254 (Merck).

2′,4′-Dihydroxy-6′-methoxymethoxyacetophenone (5) 2′,4′-Bis(benzyloxy)-6′-methoxymethoxyacetophenone (4.5 g, 11.46 mmol) was hydrogenolyzed over Pd/C (5%) (450 mg) in MeOH (100 ml) and AcOEt (100 ml) at 18—23 °C until uptake of hydrogen ceased. After removal of the solvent under reduced pressure, the resulting compound was purified by silica gel column chromatography (AcOEt : hexane = 2 : 1 as a solvent) and recrystallized from a mixture of AcOEt and hexane to give dihydroxyacetophenone **5** (2.28 g, 94%) as colorless needles, mp 118—120 °C; ^{1}H-NMR ($CDCl_3$) δ=2.65 (3H, s, $COCH_3$), 3.52 (3H, s, OCH_3), 5.25 (2H, s, OCH_2O), 5.25 (1H, s, $C_{4'}$-OH), 6.04 (1H, d, J=2.4 Hz, Ar-H), 6.14 (1H, d, J=2.4 Hz, Ar-H), 13.79 (1H, s, $C_{6'}$-OH). *Anal.* Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.61; H, 5.60.

2′,4′-Dihydroxy-3′-iodo-6′-methoxymethoxyacetophenone (6) The acetophenone **5** (3.16 g, 14.8 mmol) was dissolved in EtOH (30 ml), and iodine (1.88 g, 7.4 mmol) and periodic acid (674 mg, 3 mmol) in water (10 ml) were added to the solution; the mixture was then stirred for 30 min at 40 °C. The mixture was cooled and diluted with water to give compound **6** as colorless needles (4.63 g, 92%), mp 160—161 °C; ^{1}H-NMR ($CDCl_3$) δ=2.69 (3H, s, $COCH_3$), 3.52 (3H, s, OCH_3), 5.28 (2H, s, OCH_2O), 5.98 (1H, s, $C_{4'}$-OH), 6.44 (1H, s, $C_{5'}$-H), 14.97 (1H, s, $C_{2'}$-OH). *Anal.* Calcd for $C_{10}H_{11}IO_5$: C, 35.52; H, 3.28. Found: C, 35.23; H, 3.17.

2′,4′-Bis(benzyloxy)-3′-iodo-6′-methoxymethoxyacetophenone (7) To a mixture of **6** (1.0 g, 2.95 mmol), K_2CO_3 (2.03 g, 15 mmol), and DMF (8 ml), a solution of benzyl chloride (0.75 ml, 6.5 mmol) in DMF (1 ml) was added dropwise with stirring under nitrogen at 70 °C for 30 min. The reaction mixture was extracted with $CHCl_3$, washed with diluted HCl and water, and dried (Na_2SO_4). The resulting compound was recrystallized from a mixture of MeOH and AcOEt to yield **7** (623 mg, 80%) as colorless needles, mp 96—98 °C; ^{1}H-NMR ($CDCl_3$) δ=2.47 (3H, s, $COCH_3$), 3.46 (3H, s, OCH_3), 4.97 (2H, s, $ArCH_2O$), 5.15 (2H, s, OCH_2O), 5.18 (2H, s, $ArCH_2O$), 6.65 (1H, s, $C_{5'}$-H), 7.32—7.60 (10H, m, Ar-H×10). *Anal.* Calcd for $C_{24}H_{23}IO_5$: C, 55.61; H, 4.47. Found: C, 55.66; H, 4.48.

2,4,2′,4′-Tetrakis(benzyloxy)-3′-iodo-6′-methoxymethoxychalcone (8) and 2,4,2′,4′-Tetrakis(benzyloxy)-6′-hydroxy-3′-iodochalcone (9) A mixture of the acetophenone **7** (1.84 g, 3.54 mmol) and 2,4-bis(benzyloxy)-benzaldehyde (1.70 g, 5.3 mmol) was stirred in the presence of KOH (2.0 g, 35 mmol) in EtOH (120 ml) at 80 °C for 45 min. Ice-water and 10% HCl were added to the reaction mixture to give 6′-methoxymethoxychalcone **8** as yellow precipitates. The collected crude solid **8** was dissolved in a mixture of $CHCl_3$ (60 ml) and MeOH (60 ml). Concentrated HCl (3 ml) was added to the solution, and then the mixture was stirred at 40 °C for 1 h. The whole solution was extracted with $CHCl_3$, and the chloroform extract was washed with water and dried (Na_2SO_4). After removal of the solvent, the resulting compound was recrystallized from a mixture of $CHCl_3$ and MeOH to give 6′-hydroxychalcone **9** (2.35 g, 86% from **7**) as yellow needles, mp 158—160 °C; ^{1}H-NMR ($CDCl_3$) δ=4.82, 5.00, 5.07, and 5.20 (each 2H, s, $Ph\underline{CH_2}$), 6.38 (1H, dd, J=2.4 and 8.8 Hz, C_5-H), 6.41 (1H, s, $C_{5'}$-H), 6.54 (1H, d, J=2.4 Hz, C_3-H), 7.1—7.53 (21H, m, Ar-H×20, C_6-H), 7.90, and 8.29 (each 1H, d, J=15.6 Hz, CH=), 13.77 (1H, s, C_2-OH). *Anal.* Calcd for $C_{43}H_{35}IO_6$: C, 66.67; H, 4.55. Found: C, 66.43; H, 4.62.

6′-Acetoxy-2,4,2′,4′-tetrakis(benzyloxy)-3′-iodochalcone (10) and 2′,4′,5,7-Tetrakis(benzyloxy)-6-iodoisoflavone (12) The chalcone **9** (540 mg, 0.70 mmol) was converted into acetate **10** at 70 °C for 30 min using an acetic anhydride (20 ml)-pyridine (2 ml) method. After the addition of water to the reaction mixture, the whole mixture was extracted with $CHCl_3$ and the extract was washed with water and dried (Na_2SO_4). After the resulting acetate **10** (530 mg) and TTN (420 mg, 0.9 mmol) were stirred in a solution of MeOH (25 ml) and $CHCl_3$ (10 ml) at 30 °C for 4 h, 10% HCl (15 ml) was added to the reaction mixture, and the whole solution was stirred at room temperature for 1 h to give white precipitates. After removal of the precipi-

tates by filtration, the filtrate was extracted with $CHCl_3$, and the extract was washed with water and dried (Na_2SO_4). The resulting crude acetal **11** in dioxane (10 ml) and MeOH (10 ml) was stirred with 10% aqueous NaOH (8 ml) at room temperature for 2 h, and then water and 10% HCl were added to the reaction mixture to give precipitates. The collected precipitates were extracted with $CHCl_3$, washed with water, and dried (Na_2SO_4). The resulting compound was chromatographed over a silica gel flash column ($CHCl_3$ as a solvent) to give the isoflavone **12** (218 mg, 40% from **9**), and recrystallized from a solution of MeOH and $CHCl_3$) as pale yellow needles, mp 174—176.5 °C.

2,4,2′,4′-Tetrakis(benzyloxy)-6′-benzoyloxy-3′-iodochalcone (13) A mixture of the chalcone **9** (3.0 g, 3.87 mmol), benzoyl chloride (0.68 ml, 5.9 mmol), and K_2CO_3 (2.68 g, 19 mmol) in DMF (35 ml) was stirred under nitrogen at 60 °C for 30 min. After removal of K_2CO_3 and the solvent under reduced pressure, the residue was extracted with $CHCl_3$, washed with 10% HCl and water, and dried (Na_2SO_4). The resulting compound was purified by silica gel column chromatography ($CHCl_3$: hexane = 10 : 1 as a solvent) and further recrystallized from MeOH–Me_2CO to give **13** (3.18 g, 92%) as pale yellow needles, mp 126—128 °C; ^{1}H-NMR ($CDCl_3$) δ=4.99, 5.01, 5.04, and 5.18 (each 2H, s, Ph$\underline{CH_2}$), 6.51 (1H, s, C_3-H), 6.53 (1H, s, C_5-H), 6.77 (1H, s, $C_{5'}$-H), 7.03 and 7.79 (each 1H, d, J=16.1 Hz, CH=), 7.20—8.10 (25H, m, Ar-H×25). *Anal.* Calcd for $C_{50}H_{39}IO_7$: C, 68.34; H, 4.47. Found: C, 68.13; H, 4.70.

1-[6-Benzoyloxy-2,4-bis(benzyloxy)-3-iodophenyl]-2-[2,4-bis(benzyloxy)phenyl]-3,3-dimethoxypropan-1-one (14) and 2,4,2′,4′-Tetrakis(benzyloxy)-6-iodoisoflavone (12) A mixture of the chalcone **13** (1.61 g, 1.83 mmol) and TTN (1.24 g, 2.8 mmol) was stirred in a solution of MeOH (150 ml) and $CHCl_3$ (60 ml) at 40 °C for 4 h, then 10% HCl (35 ml) was added to the mixture at room temperature and the whole was further stirred at that temperature for 1 h to give white precipitates. After removal of the precipitates by filtration, the filtrate was extracted with $CHCl_3$ and the extract was washed with water and dried (Na_2SO_4). The organic solvent was removed under reduced pressure, and the resulting crude acetal **14** was dissolved in a mixture of dioxane (80 ml) and MeOH (100 ml), and then hydrolyzed with 10% aqueous NaOH at room temperature for 2 h. Water and 10% HCl were added to the reaction mixture to give precipitates. The collected precipitates were extracted with $CHCl_3$, washed with water, and dried (Na_2SO_4). The resulting compound was chromatographed over a silica gel column ($CHCl_3$ as a solvent) to give the 6-iodoisoflavone **12**, which was recrystallized from a mixture of MeOH and $CHCl_3$ as pale yellow needles (995 mg, 70% from **13**), mp 174—176 °C; ^{1}H-NMR ($CDCl_3$) δ=5.02, 5.03, 5.05, and 5.25 (each 2H, s, Ph$\underline{CH_2}$), 6.63 (1H, dd, J=2.4 and 8.5 Hz, $C_{5'}$-H), 6.67 (1H, d, J=2.4 Hz, $C_{3'}$-H), 6.73 (1H, s, C_8-H), 7.20—7.75 (21H, m, Ar-H×21), 7.78 (1H, s, C_2-H). *Anal.* Calcd for $C_{43}H_{33}IO_6$: C, 66.85; H, 4.30. Found: C, 66.64; H, 4.58.

Acetal **14**: mp 56—58 °C; ^{1}H-NMR ($CDCl_3$) δ=2.92 and 3.14 (each 3H, s, OCH_3), 4.7—5.0 (6H, m, Ph$\underline{CH_2}$×3), 5.09 (2H, s, Ph$\underline{CH_2}$), 5.15 and 5.47 (each 1H, d, J=8.8 Hz, CH), 6.25 (1H, dd, J=3 and 8.6 Hz, Ar-H), 6.37 (1H, d, J=3 Hz, Ar-H), 6.54 (1H, s, Ar-H), 7.09 (1H, d, J=8.6 Hz, Ar-H), 7.05—8.15 (25H, m, Ar-H×25).

2′,4′,5,7-Tetrakis(benzyloxy)-6-(3-hydroxy-3-methyl-1-butynyl)isoflavone (15) To a solution of **12** (1.5 g, 1.94 mmol) and 2-methyl-3-butyn-2-ol (0.56 ml, 6 mmol) in a mixture of NEt_3 (25 ml) and DMF (9 ml), were added $PdCl_2$ (17 mg, 0.1 mmol), PPh_3 (51 mg, 0.19 mmol), and CuI (18 mg, 0.1 mmol); the mixture was then stirred under nitrogen at 75 °C for 2 h. The reaction mixture was filtered through charcoal and the filtrate was concentrated under reduced pressure and extracted with AcOEt; the extract was then washed with 2% HCl and water and dried (Na_2SO_4). The resulting compound was purified by silica gel column chromatography ($CHCl_3$: AcOEt = 10 : 1 as a solvent) and further recrystallized from a mixture of MeOH and Me_2CO to give **15** (1.32 g, 71%) as colorless prisms, mp 173—174°C; ^{1}H-NMR ($CDCl_3$) δ=1.51 (6H, s, CH_3×2), 5.04, 5.06, 5.15, and 5.20 (each 2H, s, Ph$\underline{CH_2}$), 6.68 (1H, d, J=2.4 Hz, $C_{3'}$-H), 6.69 (1H, s, C_8-H), 7.20—7.70 (21H, m, Ar-H×21), 7.77 (1H, s, C_2-H). *Anal.* Calcd for $C_{48}H_{40}O_7$: C, 79.10; H, 5.53. Found: C, 78.86; H, 5.63.

2′,4′,5,7-Tetrahydroxy-6-(3-hydroxy-3-methylbutyl)isoflavone (Luteone Hydrate) (2) The isoflavone **15** (2.31 g, 3.17 mmol) was hydrogenolyzed over Pd/C (5%) (400 mg) in MeOH (120 ml) and dioxane (100 ml) at room temperature until uptake of hydrogen ceased. After removal of the solvent under reduced pressure, the resulting compound was recrystallized from a mixture of MeOH and CH_2Cl_2 to give **2** (1.13 g, 96%) as pale yellow prisms, mp 229—231 °C; IR (KBr) ν 3350, 2975, 1645, 1620, 1460, 1310, 1065, and 830 cm^{-1}; UV λ_{max} nm (log ε) (MeOH) 265 (4.45), 290sh (4.19), and 347sh (3.58); (+$AlCl_3$) 208sh (3.53), 240sh (4.10), and 267 (4.46); (+NaOAc) 273sh, 269 (4.44), and 340 (3.93). *Anal.* Calcd for $C_{20}H_{20}O_7$: C, 64.51, H, 5.41. Found: C, 64.22; H, 5.46.

2′,4′,7-Tris(benzoyloxy)-5-hydroxy-6-(3-hydroxy-3-methylbutyl)isoflavone (16) A mixture of **2** (420 mg, 1.12 mmol), benzoyl chloride (0.47 ml, 4 mmol), and K_2CO_3 (1.55 g, 11 mmol) in Me_2CO (20 ml) was refluxed with stirring under nitrogen for 30 min. After removal of K_2CO_3 and the solvent, the residue was extracted with ethyl acetate, washed with 5% HCl and water, and dried (Na_2SO_4). The resulting compound was purified by silica gel column chromatography ($CHCl_3$: Me_2CO = 10 : 1 as a solvent) and further recrystallized from a mixture of MeOH and AcOEt to give **16** (650 ml, 85%) as pale yellow needles, mp 154—155 °C; ^{1}H-NMR ($CDCl_3$) δ=1.19 (6H, s, CH_3×2), 1.69 and 2.72 (each 2H, m, CH_2), 6.84 (1H, s, C_8-H), 7.26—7.70 (13H, m, Ar-H×13), 7.98 (1H, s, C_2-H), 8.1—8.25 (5H, m, Ar-H×5), 12.92 (1H, s, C_5-OH). *Anal.* Calcd for $C_{41}H_{32}O_{10}$: C, 71.92; H, 4.71. Found: C, 71.91; H, 4.78.

2′,4′,7-Tris(benzoyloxy)-6-(3-hydroxy-3-methylbutyl)-5-tosyloxyisoflavone (17) A mixture of **16** (820 mg, 1.19 mmol), TsCl (342 mg, 1.8 mmol), and K_2CO_3 (1.66 g, 12 mmol) in Me_2CO (35 ml) was refluxed with stirring under nitrogen for 20 min. After removal of K_2CO_3 and the solvent, the residue was extracted with AcOEt, washed with 5% HCl and water, and dried (Na_2SO_4). The resulting compound was recrystallized from a mixture of $CHCl_3$ and MeOH to give **17** (906 mg, 91%) as colorless needles, mp 116—119 °C; ^{1}H-NMR ($CDCl_3$) δ=1.13 (6H, s, CH_3×2), 1.39 (1H, s, OH), 1.71 and 2.82 (each 2H, m, CH_2), 2.45 (3H, s, Ar-CH_3), 7.26—7.70 (15H, m, Ar-H×15), 7.87 (1H, s, C_2-H), 7.9—8.2 (8H, m, Ar-H×8). *Anal.* Calcd for $C_{48}H_{38}O_{12}S$: C, 68.73; H, 4.57. Found: C, 68.47; H, 4.76.

Dehydration of 2′,4′,7-Tris(benzoyloxy)-6-(3-hydroxy-3-methylbutyl)-5-tosyloxyisoflavone (17) with Boron Trifluoride Diethyl Etherate To a solution of **17** (50 mg, 0.06 mmol) in dry CH_2Cl_2 (2 ml) was added a solution of $BF_3 \cdot OEt_2$ (0.05 mmol) in CH_2Cl_2 (0.4 ml); the mixture was stirred under nitrogen at room temperature for 2 h. To the reaction mixture was added aqueous NH_4Cl, and the whole solution was extracted with chloroform, washed with water, and dried (Na_2SO_4). The resulting compound was chromatographed over a silica gel column ($CHCl_3$ as a solvent) to give 5-tosyloxyisoflavone **18** [10 mg (20%) as colorless needles, mp 188—189 °C], 5-hydroxyisoflavone **19** [10 mg (25%) as pale yellow needles, mp 177—179 °C], and dihydropyranoisoflavone **20** [18 mg (45%) as colorless prisms], mp 187—190 °C; ^{1}H-NMR ($CDCl_3$) δ=1.41 (6H, s, CH_3×2), 1.81 and 2.68 (each 2H, t, J=6.8 Hz, CH_2), 6.81 (1H, s, C_8-H), 7.2—7.7 (12H, m, Ar-H), 7.81 (1H, s, C_2-H), 8.09—8.23 (6H, m, Ar-H). *Anal.* Calcd for $C_{41}H_{30}O_9$: C, 73.87; H, 4.54. Found: C, 73.65; H, 4.80.

2′,4′,7-Tris(benzoyloxy)-6-(3-methyl-2-butenyl)-5-tosyloxyisoflavone (18) To a solution of **17** (1.0 g, 1.19 mmol) in dry toluene (6 ml) was added TsOH·H_2O (1.81 ml of a 5.25×10^{-1} mol dm^{-3} in acetic acid); the mixture was stirred under nitrogen at 110 °C for 45 min. The reaction mixture was extracted with ether, washed with 5% aqueous $NaHCO_3$, 2% HCl, and water, and dried (Na_2SO_4). The resulting compound was chromatographed over a silica gel-flashed column ($CHCl_3$ as a solvent) to give a mixture of 6-alkenylisoflavones (745 mg) as colorless needles. The ^{1}H-NMR spectrum of the mixture was shown to be an 85 : 15 mixture of the 6-(3-methyl-2-butenyl)isoflavone **18** and the isomer 6-(3-methyl-3-butenyl)isoflavone **21**. The mixture (**18** and **21**) in CH_2Cl_2 (0.5 ml) was added to a solution of benzohydroximoyl chloride (63 mg, 0.4 mmol) and NEt_3 (0.13 ml, 0.94 mmol) in CH_2Cl_2 (2 ml) in an ice-bath, and then the reaction mixture was stirred at room temperature for 20 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2, washed with water, and dried (Na_2SO_4). The resulting compound was chromatographed over a silica gel column ($CHCl_3$: Me_2CO = 15 : 1 as a solvent) to give the 6-prenylisoflavone **18**, which was recrystallized from a mixture of $CHCl_3$ and hexane as colorless needles (500 mg, 68% from **17**), mp 188—189 °C; ^{1}H-NMR ($CDCl_3$) δ=1.38 and 1.45 (each 3H, s, CH_3), 2.44 (3H, s, Ar-CH_3), 3.36 (2H, d, J=6.4 Hz, CH_2), 4.92 (1H, br t, J=6.4 Hz, =CH), 7.2—7.7 (15H, m, Ar-H×15), 7.86 (1H, s, C_2-H), 8.0—8.2 (8H, m, Ar-H×8). *Anal.* Calcd for $C_{48}H_{36}O_{11}S$: C, 70.23; H, 4.42. Found: C, 70.19; H, 4.59.

2′,4′,7-Tris(benzoyloxy)-5-hydroxy-6-(3-methyl-2-butenyl)isoflavone (19) A mixture of **18** (160 mg, 0.19 mmol) and BCl_3 (0.14 ml; 1 mol solution: Aldrich) on dry CH_2Cl_2 (2 ml) was stirred under argon at 15 °C for 15 min. The reaction mixture was quenched with saturated NH_4Cl and extracted with CH_2Cl_2, washed with water, and dried (Na_2SO_4). The resulting compound was purified by silica gel column chromatography ($CHCl_3$ as a solvent) and crystallized fron $CHCl_3$–hexane to give **19** (123 mg, 95%) as pale yellow needles, mp 177—179 °C; ^{1}H-NMR ($CDCl_3$) δ=1.55 and 1.59 (each 3H, s, CH_3), 3.34 (2H, d, J=7.3 Hz, CH_2), 5.12 (1H, t, J=7.3 Hz, =CH), 6.80 (1H, s, C_8-H), 7.3—7.7 (15H, m, Ar-H×15), 7.97 (1H, s, C_2-

H), 8.1—8.2 (6H, m, Ar-H×6), 12.90 (1H, s, C_5-OH). *Anal.* Calcd for $C_{41}H_{30}O_9$: C, 73.87; H, 4.54. Found: C, 73.73; H, 4.76.

2′,4′,5,7-Tetrahydroxy-6-(3-methyl-2-butenyl)isoflavone (Luteone) (1) Compound **19** (150 mg, 0.22 mmol) in MeOH (2 ml) and dioxane (2 ml) was hydrolyzed with 10% aqueous NaOH (2 ml) under argon at room temperature for 1 h. To the reaction mixture water and diluted HCl were added; the organic solvent was then evaporated under reduced pressure. The residue was extracted with ether, washed with water, and dried (Na_2SO_4). The compound was chromatographed over a silica gel column ($CHCl_3$: AcOEt=2 : 1 as a solvent) to give 6-prenylisoflavone **1** (52 mg, 66%), which was crystallized from CH_2Cl_2–hexane as pale yellow prisms, mp 223—225°C; IR (KBr) ν 3425, 3300, 3100 br., 1650, 1615, 1590, 1550, 1215, 1060, 815 cm^{-1}; UV λ_{max} nm (log ε) (MeOH) 266 (4.56), 280 (4.33), 340 (3.63), (+$AlCl_3$) 271 (4.41), (+NaOAc) 269 (4.55), 340 (3.83). *Anal.* Calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.55; H, 5.21.

2′,4′,5,7-Tetraacetoxy-6-(3-methyl-2-butenyl)isoflavone (22) Compound **1** (159 mg, 0.45 mmol) was converted into tetraacetate **22** by treatment with acetic anhydride (2 ml)-pyridine (0.3 ml) at 110 °C for 2 h. The resulting compound was purified by silica gel column chromatography (AcOEt : hexane=2 : 1 as a solvent) to give **22** as colorless pastes (188 mg, 80%); ^{1}H-NMR ($CDCl_3$) δ=1.68 and 1.75 (each 3H, s, CH_3), 2.16, 2.30, 2.36, and 2.40 (each 3H, s, $COCH_3$), 3.23 (2H, br d, CH_2), 5.00 (1H, br t, =CH), 7.04—7.29 (4H, m, Ar-H), 7.80 (1H, s, C_2-H).

4,2′,4′-Tris(benzyloxy)-6′-hydroxy-3′-iodochalcone (24) A mixture of the acetophenone **7** (300 mg, 0.58 mmol) and 4-benzyloxybenzaldehyde (188 mg, 0.9 mmol) in EtOH (50 ml) was stirred in the presence of KOH (330 mg, 6 mmol) at 80 °C for 1 h. The resulting 6′-methoxymethoxychalcone **23** was worked up in the same manner as in the case of the 6′-hydroxychalcone **8** to 6′-hydroxy-4-benzyloxychalcone **24**, which was recrystallized from a mixture of $CHCl_3$ and MeOH as yellow needles (334 mg, 87% *via* two steps from **7**), mp 124—125 °C; ^{1}H-NMR ($CDCl_3$) δ=4.86, 5.10 and 5.21 (each 2H, s, Ph$\underline{CH_2}$), 6.24 (1H, s, C_5-H), 6.84 (2H, d, J=8.8 Hz, C_3- and C_5-H), 6.99—7.53 (17H, m, Ar-H), 7.83 and 7.88 (each 2H, d, J=15.4 Hz, CH=), 13.57 (1H, s, C_6-OH). *Anal.* Calcd for $C_{36}H_{29}IO_5$: C, 64.68; H, 4.37. Found: C, 64.47; H, 4.61.

4′,5,7-Tris(benzyloxy)-6-iodoisoflavone (27) A mixture of **24** (300 mg, 0.45 mmol), benzoyl chloride (0.08 ml, 0.7 mmol), and K_2CO_3 (433 mg, 3.1 mmol) in DMF (8 ml) was stirred under the same conditions as in the case of the benzoate **13** to give 6′-benzoyloxy-3′-iodochalcone **25**. A mixture of **25** and TTN (300 mg, 0.68 mmol) was stirred in a solution of MeOH (25 ml) and $CHCl_3$ (10 ml) at 40 °C for 20 h. The resulting crude acetal **26** in dioxane (10 ml) and MeOH (10 ml) was hydrogenated with 10% aqueous NaOH at room temperature for 2 h. The reaction mixture was worked up in the same manner as in the case of the 6-iodoisoflavone **12** to give 4′,5,7-tris(benzyloxy)-6-iodoisoflavone **27**, which was recrystallized from a mixture of $CHCl_3$ and MeOH as pale yellow needles (86 mg, 30% *via* three steps from **24**), mp 154—157 °C; ^{1}H-NMR ($CDCl_3$) δ=5.07, 5.10 and 5.27 (each 2H, s, Ph$\underline{CH_2}$), 6.75 (1H, s, C_8-H), 7.04 (2H, d, J=8.8 Hz, $C_{3'}$- and $C_{5'}$-H), 7.30 (15H, m, Ar-H), 7.77 (2H, d, J=8.8 Hz, $C_{2'}$- and $C_{6'}$-H), 7.81 (1H, s, C_2-H). *Anal.* Calcd for $C_{37}H_{27}IO_5$: C, 64.87; H, 4.08. Found: C, 64.65; H, 4.23.

4′,5,7-Tris(benzyloxy)-6-(3-hydroxy-3-methylbutynyl)isoflavone (28) To a solution of **27** (640 mg, 0.96 mmol) and 2-methyl-3-butyn-2-ol (0.28 ml, 3 mmol) in a mixture of NEt_3 (15 ml) and DMF (5 ml) were added $PdCl_2$ (8.5 mg, 0.05 mmol), PPh_3 (25 mg, 0.1 mmol), and CuI (9.1 mg, 0.05 mmol); the mixture was then stirred under nitrogen at 80 °C for 1 h. The reaction mixture was worked up in the same manner as in the case of the 6-alkynylisoflavone **15** to give 6-(3-hydroxy-3-methylbutynyl)isoflavone **28**, which was recrystallized from a mixture of MeOH and Me_2CO as colorless needles (340 mg, 57%), mp 171—173 °C; ^{1}H-NMR ($CDCl_3$) δ=1.50 (6H, s, CH_3×2), 1.78 (1H, s, OH), 5.10 and 5.21 (6H, s, Ph$\underline{CH_2}$×3), 6.72 (1H, s, C_8-H), 7.03 (2H, d, J=8.3 Hz, $C_{3'}$- and $C_{5'}$-H), 7.30—7.52 (15H, m, Ar-H), 7.67 (2H, d, J=8.3 Hz, $C_{2'}$- and $C_{6'}$-H), 7.79 (1H, s, C_2-H). *Anal.* Calcd for $C_{41}H_{34}O_6$: C, 79.08; H, 5.50. Found: C, 78.94; H, 5.53.

4′,5,7-Trihydroxy-6-(3-hydroxy-3-methylbutyl)isoflavone (Wighteone Hydrate) (3) The isoflavone **28** (720 mg, 1.15 mmol) in a solution of MeOH (30 ml) and dioxane (30 ml) was hydrogenolyzed over Pd/C (5%) (80 mg) at room temperature until uptake of hydrogen ceased. The resulting compound was recrystallized from a mixture of water and MeOH to give **3** (367 mg, 92%) as colorless needles, mp 230—232 °C (lit.,[7] 225—228 °C); ^{1}H-NMR (see Table 1). *Anal.* Calcd for $C_{20}H_{20}O_6$: C, 67.41; H, 5.66. Found: C, 67.22; H, 5.48.

4′,7-Diacetoxy-5-hydroxy-6-(3-hydroxy-3-methylbutyl)coumarono-chromone (29) To a dioxane solution (12 ml) of the 2′-hydroxyisoflavone **2** (350 mg; 0.93 mmol), *o*-chloranil (303 mg, 1.2 mmol) was added and stirred at 80 °C for 10 min, and subsequently *o*-chloranil (305 mg, 1.2 mmol) was again added to the mixture, and the whole was stirred at 80 °C for 2 h. After removal of the solvent, unreacted *o*-chloranil was removed by silica gel column chromatography (AcOEt : $CHCl_3$=2 : 1 as a solvent) and the obtained coumaronochromone **4** was converted into the diacetate **29** by treatment with acetic anhydride (20 ml)–pyridine (1.5 ml) at 0 °C for 30 min. The resulting compound was purified by silica gel column chromatography (AcOEt : $CHCl_3$=2 : 1 as a solvent) to give **29** (205 mg, 61% *via* two steps from **2**) as colorless needles, mp 271—274 °C; ^{1}H-NMR ($CDCl_3$) δ=1.31 (6H, s, CH_3×2), 1.55 (1H, s, OH), 1.71 and 2.73 (each 2H, m, CH_2), 2.36 and 2.39 (each 3H, s, $COCH_3$), 6.87 (1H, s, C_8-H), 7.20 (1H, dd, J=1.9 and 8.3 Hz, $C_{5'}$-H), 7.39 (1H, d, J=1.9 Hz, $C_{3'}$-H), 8.08 (1H, d, J=8.3 Hz, $C_{6'}$-H), 13.16 (1H, s, C_5-OH). *Anal.* Calcd for $C_{24}H_{22}O_9$: C, 63.43; H, 4.88. Found: C, 63.53; H, 4.85.

4′,5,7-Trihydroxy-6-(3-hydroxy-3-methylbutyl)coumaronochromone (4) Compound **29** (120 mg, 0.26 mmol) in a mixture of MeOH–dioxane was hydrolyzed with 10% aqueous NaOH at room temperature for 1 h. The resulting compound was recrystallized from a mixture of H_2O and MeOH to give **4** (66 mg, 67%) as colorless needles, mp 260—262 °C; ^{1}H-NMR (DMSO-d_6) δ=1.16 (6H, s, CH_3×2), 1.52 and 2.61 (each 2H, m, CH_2), 4.18 (1H, br s, OH), 6.61 (1H, s, C_8-H), 6.92 (1H, dd, J=2.0 and 8.9 Hz, $C_{5'}$-H), 7.11 (1H, d, J=2.0 Hz, $C_{3'}$-H), 7.74 (1H, d, J=8.9 Hz, $C_{6'}$-H), 9.94 and 10.80 (each 1H, br s, OH), 13.13 (1H, s, C_5-OH). *Anal.* Calcd for $C_{20}H_{18}O_7$: C, 64.86; H, 4.90. Found: C, 64.69; H, 4.82.

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