Regioselective Synthesis of Natural 6-Prenylpolyhydroxyisoflavone (Lupisoflavone) and Lupisoflavone Hydrate with Hypervalent Iodine Reagents

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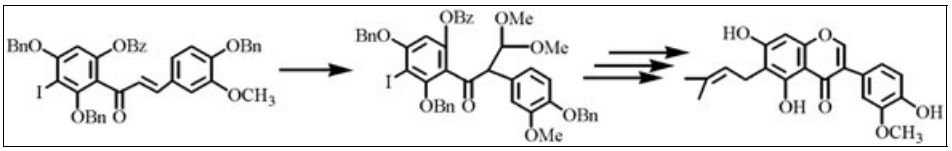

The Pd(0)-catalyzed coupling reaction of 6-iodotetraalkoxyisoflavone, which was obtained from the oxidative rearrangement of 3′-iodotetraalkoxychalcones, with 2-methyl-3-butyn-2-ol in heating condition affords 6-alkynylisoflavone. Hydrogenation of 6-iodotetraalkoxyisoflavone followed by acid-catalyzed dehydration with *p*-TsOH·H_2O gave lupisoflavone.

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INTRODUCTION

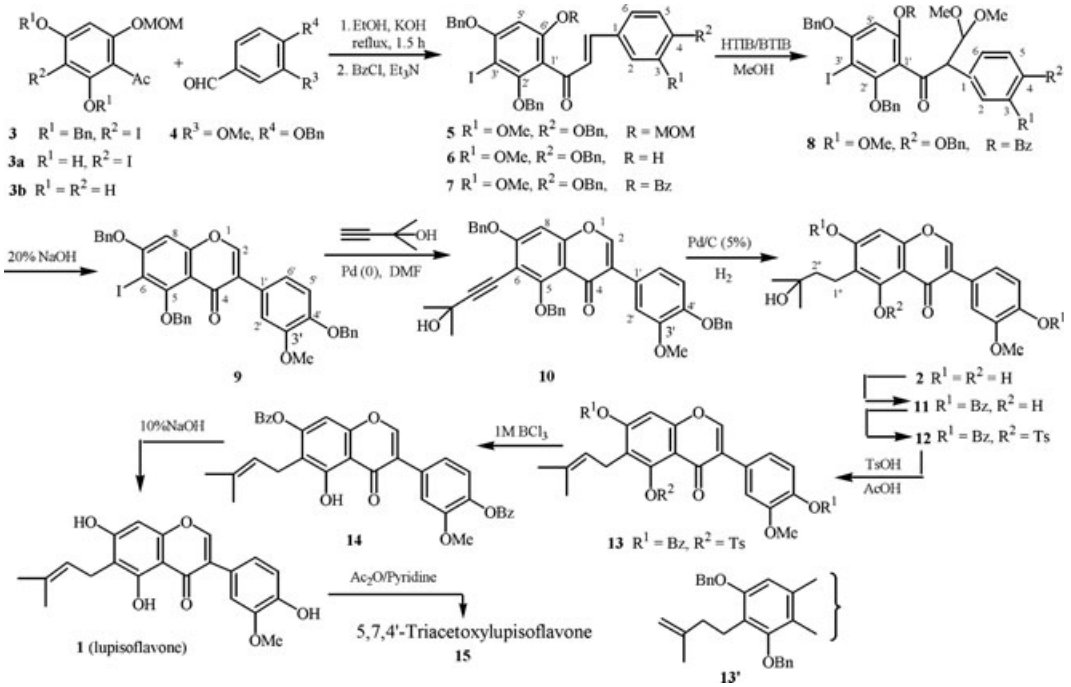
Isoflavones have been isolated mainly from leguminous plants. The occurrence of isoflavone aglycones is almost restricted to the Leguminosae family, despite their large structural variation [1]. The structural diversity arises from the different oxidation levels and also from the number and complexity of substituents in both the ring system [2, 3]. Besides, isoflavones are very important as precursors of prenylisoflavones and pterocarpans. Prenylated isoflavones are known as complex isoflavones having additional carbon chain (dimethylallyl or geranyl) as acyclic or cyclic side chains [4] to the basic C15 isoflavonoid skeleton. Isoflavones in addition, exhibit phytoalexin [5], antifungal, anti-inflammatory [6], antioxidant, and anticancer [7] properties. Hence, isoflavones have attracted considerable attention in recent years. Lupisoflavone, **1**, a prenylated isoflavone, was first isolated as a minor constituent from the leaf extract of white lupin (*Lupinus albus*) and the structure was deduced as 5,7,4′-trihydroxy-6-(3-methyl-2-butenyl)-3′-methoxyisoflavone with the help of only ^{1}H NMR analysis [8, 9]. Since lupisoflavone was isolated as little quantity, the study about its structural feature was not done exclusively. However, it was found that it shows moderate antifungal [8] activity.

Meanwhile, another important bioactivity of lupisoflavone has been reported. It is reported that lupisoflavone induces the conversion of both the C1 and C2 cell wall isoperoxidases to the C5 isoperoxidases, which possess scopoletin-peroxidase [10] activity. The total synthesis of lupisoflavone and its hydrate together with some other important complex isoflavones was reported for the first time ever using microwave-irradiation technique [11]. The regioselective and direct introduction of alkenyl or alkyl group at the 6-position of isoflavone skeleton is relatively difficult because of its easy isomerization of 6-alkylpolyhydroxyisoflavones into 8-alkylpolyhydroxyisoflavones by bases [12, 13]. Generally, isoflavones are synthesized by oxidative rearrangement of chalcones with Tl(III)$(NO_3)_3\cdot 3H_2O$, thallium(III) nitrate trihydrate (TTN) [14, 15]. However, the yield [16] of the product in this method was found to be very low. Furthermore, TTN is toxic, hygroscopic, and has adverse effects on the environment. As reported, hypervalent iodine reagents such as [hydroxyl(toxyloxy)iodo]benzene (HTIB) [17] and [bis(trifluoroacetoxy)iodo]benzene (BTIB) [18] have become more useful for the oxidative rearrangement of chalcones. Using HTIB/BTIB, far better results were obtained for the conversion of chalcone to acetal [19] and then isoflavone. It is worth noting that unlike TTN, hypervalent iodine reagents are environmentally friendly and ease of handling [20]. In continuation of the studies on the synthesis of prenylisoflavones, I report here the total synthesis of lupisoflavone **1** and lupisoflavone hydrate **2** from the corresponding 3′-iodochalcone using both HTIB and BTIB using conventional heating.

RESULTS AND DISCUSSION

The introduction of iodine at the 3′-position of 6′-methoxymethoxyacetophenone **3b**, obtained by the catalytic hydrogenation (5% Pd/C) of 2′,4′-bis(benzyloxy)-6′-methoxymethoxyacetophenone [13], was carried out with iodine and periodic acid [16, 21] to give the desired 3′-iodoacetophenone **3a** in 94% yield. The benzylation of compound **3a** with benzyl chloride in the presence of

Scheme 1



K_2CO_3 in dimethyl formamide (DMF) afforded 2′,4′-bis (benzyloxy)-3′-iodoacetophenone **3** in 82% yield. Condensation of **3** with 4-benzyloxy-3-methoxybenzaldehyde (**4**) in the presence of alcoholic KOH solution gave 6′-methoxymethoxychalcone **5** (Scheme 1). 6′-Hydroxychalcone **6** was obtained from the crude compound **5** by concentrated HCl-mediated hydrolysis in a mixture of methanol and chloroform in 73% yield (via two steps from **3**). A crucial oxidative rearrangement of 6′-benzoyloxychalcone **7**, prepared by benzoylation of compound **6**, with HTIB/BTIB in a mixture of methanol and chloroform gave the crude acetal **8**. The structure of acetal **8** was determined by ^{1}H NMR [δ 3.10 and 3.24, $CH(OCH_3)_2$]. The subsequent hydrolysis of crude acetal **8** with aqueous 20% NaOH and *in situ* ring closing reaction afforded the desired 6-iodoisoflavone **9** in 47% yields (via two steps from **7**). It should be mentioned here that the yield of iodoisoflavone was found to be 32% in the case of BTIB. This is presumably due to the lower dissociation rate of BTIB compared with HTIB, slows down the reaction. The Sonogashira *et al.*[22] coupling reaction of **9** with 2-methyl-3-butyn-2-ol in the presence of Pd(0) in a mixture of Et_3N and DMF gave 6-(3-hydroxy-3-methylbutynyl)isoflavone **10** in 74% yield. The quantitative catalytic hydrogenation/hydrogenolysis of **10** with 5% Pd/C in a mixture of methanol and dioxane afforded 4′,5,7-trihydroxy-3′-methoxy-6-(3-hydroxy-3-methylbutyl)isoflavone **2** in 93% yield. Compound **2** (lupisoflavone hydrate) could be a natural product because the other similar type of compound such as wighteone hydrate was found as a naturally obtained compound [11]. The exhaustive benzoylation of **2** by bases in prolonged reaction time causes the isomerization of 6-alkylpolyhydroxyisoflavone to 8-alkylpolyhydroxyisoflavone [12, 13]. Therefore, the partial benzoylation of **2** was achieved in acetone at 45°C for 20 min to give the 5-hydroxyisoflavone **11** in 86% yield. The tosylation of **11** under reflux in acetone for 2 h gave 5-tosylated isoflavone **12** in 82% yields. Compound **12** was dehydrated with $TsOH{\cdot}H_2O$ in a solution of acetic acid and toluene under reflux for 1.5 h to give a mixture of the desired 6-prenylisoflavone **13** and the regioisomer, 6-(3-methyl-3-butenyl)isoflavone **13′**. The ^{1}H NMR spectrum of the alkenyl mixture (**13**:**13′**) showed the ratio of **13** to **13′** to be 77:23 [peaks due to $CH_2CH\,C(CH_3)_2$ at δ 3.35 (2H, d) and $CH_2CH_2C(CH_3)\,CH_2$ at δ 4.48 (each 1H, s)]. The treatment of the regioisomeric mixture (**13** and **13′**) with benzohydroximoyl chloride in dry dichloromethane at room temperature gave a mixture of the unchanged 6-prenylisoflavone **13** and the terminal alkene-cyclic adduct, and then the required **13** was separated by silica-gel column chromatography in 51% yield. The detosylation of **13** with 1*M* BCl_3 solution in dichloromethane at room temperature gave 5-hydroxyisoflavone **14** in 94% yield. The hydrolysis of **14** with 10% NaOH in an equal mixture of methanol and dioxane at room temperature gave 5,7,4′-trihydroxy-3′-methoxy-6-(3-methyl-2-butenyl)isoflavone **1** in 62% yield. The spectral data and other physical properties of **1** corresponded well with those of the natural sample of the lupisoflavone (Table 1) [8]. On the basis of these results, the structure of lupisoflavone was confirmed by the synthesis of 5,7,4′-trihydroxy-3′-methoxy-6-(3-methyl-2-butenyl)isoflavone **1**. Synthetic lupisoflavone was derivatized into 6-prenyltriacetoxyisoflavone **15**.

Table 1

^{1}H NMR (400 Mz, CD_3OCD_3) data for synthesized 6-prenyl-and-alkylisoflavones **1**, and **2**, and naturally obtained lupisoflavone.

Compound	2-H	8-H	2′-H	6′-H	5′-H	Me	CH_2	CH	OCH_3	OH
1	8.19s	6.50s	7.25d	7.05dd	6.89d	1.65s	3.36d	5.27 br. t	3.88s	7.77s
			J = 2.0 Hz [1H]	*J* = 8.3 and 2.0 Hz [1H]	*J* = 8.3 Hz [1H]	1.78s	*J* = 7.1 Hz		OCH_3 [3H]	9.70s 13.35s
Natural product [8] **1**	8.19s	6.52s	7.25d	7.056dd	6.89d	1.65s	3.36d	5.27 br. t	3.89s	13.35s
			J = 2.4 Hz [1H]	*J* = 8.3 and 2.4 Hz [1H]	*J* = 8.3 Hz [1H]	1.78s	*J* = 7.1 Hz		OCH_3 [3H]	
2	8.18s	6.47s	7.25d *J* = 2.0 Hz [1H]	7.05dd *J* = 8.3 and 2.0 Hz [1H]	6.89d *J* = 8.3 Hz [1H]	1.26s [6H]	1.71m 2.78m		3.88s OCH_3 [3H]	13.34s

s, singlet; d, doublet; t, triplet; dd, doublet of doublet, m, multiplet; br, broad.

EXPERIMENTAL

All the melting points were taken on a Yanaco MP-J3 micro-melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded with a JEOL EX-400 spectrometer (400 MHz) using tetramethylsilane as internal standard. The IR spectra were obtained on Hitachi 260-10 spectrophotometer using KBr pellets. The UV spectra were obtained on Hitachi U-2000 spectrophotometer. Elemental analyses were obtained on Yanaco CHN corder model MT-5. Column chromatography and thin-layer chromatography (TLC) were carried out with Kieselgel 60 (70–230 mesh) and Kieselgel 60 G-254 (Merck).

2′,4′-Dihydroxy-6′-methoxymethoxyacetophenone (3b). The palladium–carbon-catalyzed hydrogenolysis of 2′,4′-bis(benzyloxy)-6′-methoxymethoxyacetophenone (4.8 g, 12.24 mmol) in a mixture of MeOH (100 mL) and AcOEt (100 mL) was carried out at 20°C until the uptake of hydrogen ceased. The solvent was removed under reduced pressure, and the resulting compound was recrystallized from a mixture of AcOEt and hexane to give **3b** as colorless crystals, 2.48 g (95%), mp 117–119°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), 6.04 (1H, d, *J* = 2.4 Hz, ArH), 6.14 (1H, d, *J* = 2.4 Hz, ArH), 13.79 (1H, s, C_2'-OH), C_2'-OH was not observed due to exchange; 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 (3a). Compound **3b** (3.75 g, 17.61 mmol) was dissolved in ethanol (80 mL), followed by the successive addition of iodine (2.22 g, 8.74 mmol) and periodic acid (806 mg, 3.53 mmol in water, 9 mL). The reaction mixture was stirred for 1 h at 40°C. Cooling and diluting the reaction mixture with water gave a crystalline solid, which was recrystallized from the mixture of AcOEt an hexane to give **3a** as pale yellow needles, 5.59 g (94%), mp 162–164°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), 6.65 (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, 35.32; H, 3.17.

2′,4′-Bis(benzyloxy)-3′-iodo-6′-methoxymethoxyacetophenone (3). A solution of benzyl chloride (4.1 g, 32.41 mmol) in DMF (5 mL) was added slowly to a mixture of **3a** (5.0 g, 14.79 mmol) and K_2CO_3 (10 g, 72.46 mmol) in DMF (50 mL) under nitrogen. The reaction mixture was heated at 70°C for 1 h, then cooled to room temperature (rt), and extracted with $CHCl_3$. The extract was washed with 5% HCl and water and dried (Na_2SO_4), and the solvent was removed. The residue was recrystallized from a mixture of AcOEt and MeOH to give **3** as colorless needles, 6.30 g (82%), mp 98–99°C; ^{1}H NMR ($CDCl_3$): δ 2.47 (3H, s, $COCH_3$), 3.46 (3H, s, OCH_3), 4.97 (2H, s, $PhCH_2$), 5.15 (2H, s, OCH_2O), 5.18 (2H, s, $PhCH_2$), 6.65 (1H, s, C_5'-H), 7.32-7.65 (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.

4,2′,4′-Tris(benzyloxy)-3′-iodo-3-methoxy-6′-methoxy methoxychalcone (5) and 4,2′,4′-tris(benzyloxy)-6′-hydroxy-3′-iodo-3-methoxychalcone (6). A mixture of **3** (5.0 g, 9.64 mmol) and 4-benzyloxy-3-methoxybenzaldehyde (2.42 g, 10.0 mmol) was dissolved in alcoholic KOH (5.40 g, 96.2 mmol in 150 mL of EtOH). The reaction mixture was refluxed for 1 h and monitored by TLC to establish completion. The reaction mixture was neutralized with 10% HCl and extracted with $CHCl_3$, and the solvent was removed under reduced pressure to give a yellow semisolid mass of 6′-methoxymethoxychalcone **5**, which was hydrolyzed with concentrated HCl in a mixture of MeOH (100 mL) and $CHCl_3$ (100 mL) at 40°C for 1 h. The hydrolyzed mixture was allowed to cool to rt, extracted with $CHCl_3$, washed with water, and dried (Na_2SO_4). The solvent was removed under reduced pressure to give a solid mass, which was recrystallized from $CHCl_3$ and AcOEt to give 6′-hydroxychalcone **6** as colorless needles, 4.91 g (73% two steps yield from **3**), mp 133–134°C; ^{1}H NMR ($CDCl_3$): δ 3.66 (3H, s, OCH_3), 4.82 (2H, s, $PhCH_2$), 5.20 (4H, s, $PhCH_2$ × 2), 6.42 (1H, s, C_5'-H), 6.76 (1H, d, *J* = 8.3 Hz, C_5-H), 6.82 (1H, d, *J* = 1.7 Hz, C_2-H), 6.91 (1H, dd, *J* = 8.3Hz and *J* = 1.7 Hz, C_6-H), 7.15–7.52 (15H, m, Ar-H × 15), 7.81 and 7.86 (each 1H, d, *J* = 15.3 Hz, CH), 13.77 (1H, s, C_6'-OH); Anal. Calcd. for $C_{37}H_{31}IO_6$: C, 63.62; H, 4.47; Found: C, 63.47.66; H, 4.63.

4,2′,4′-Tris(benzyloxy)-6′-benzoyloxy-3′-iodo-3-methoxychalcone (7). Benzoyl chloride (1.73 g, 12.3 mmol) was slowly added to a mixture of chalcone **6** (5.60 g, 8.02 mmol) and K_2CO_3 (8.60 g, 62.2 mmol) in DMF (35 mL). The reaction mixture was heated between 60–70°C under nitrogen for 40 min and filtered of K_2CO_3. Then the filtrate was neutralized with 5% HCl, extracted with $CHCl_3$, washed with water, and dried (Na_2SO_4). After removal of the solvent, a pale yellow crude mass was obtained. The crude was purified on silica-gel column chromatography ($CHCl_3$:Hexane; 3:2) and gave **7** as a fluffy crystalline solid, 5.91 g (92%), mp 65–68°C; ^{1}H NMR ($CDCl_3$): δ 3.84 (3H, s,

OCH_3), 4.98, 5.21, and 5.32 (each 2H, s, $PhCH_2$), 6.76 (1H, s, C_5'-H), 6.81 (1H, d, J = 8.3 Hz, C_5-H), 6.85 (1H, d, J = 1.7 Hz, C_2-H), 6.91 (1H, dd, J = 8.3 Hz and J = 1.7 Hz, C_6-H), 7.25–7.59 (20H, m, Ar-H × 20), 6.90 and 6.94 (each 1H, d, J = 15.8 Hz, CH); Anal. Calcd. for $C_{44}H_{35}IO_7$: C, 65.84; H, 4.58; Found: C, 65.73.66; H, 4.38.

1-[6-Benzoyloxy-2,4-bis(benzyloxy)-3-iodophenyl]-2-(4-benzyloxy-3-methoxyphenyl)-3,3-dimethoxypropan-1-one (8) and 5,7,4′-tris(benzyloxy)-6-iodo-3′-methoxyisoflavone (9). Compound **7** (8.35 g, 10.41 mmol) was dissolved in a mixture of MeOH (90 mL) and $CHCl_3$ (20 mL) followed by the addition of HTIB (5.55 g, 14.11 mmol). The reaction mixture was stirred at rt under nitrogen for 20 h. The excess HTIB was decomposed with 5% Na_2SO_3 solution, and then the reaction mixture was extracted with $CHCl_3$, washed with water, and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave crude acetal (**8**) as a semisolid mass, which was dissolved in a mixture of MeOH (70 mL) and $CHCl_3$ (20 mL) followed by the addition of 20% aqueous NaOH (40 mL) and stirred at 25°C for 30 min. The reaction mixture was neutralized with 10% aqueous HCl, extracted with $CHCl_3$, washed with water, and dried (Na_2SO_4). The solvent was removed under reduced pressure to give a yellow solid. The crude solid was purified by column chromatography (CH_2Cl_2:Hexane; 3:1) and further recrystallized from a mixture of AcOEt and MeOH (1:1) to give 6-iodoisoflavone **9**, 3.41 g (47% two steps yields from **7**), mp 199–200°C; ^{1}H NMR ($CDCl_3$):δ 3.92 (3H, s, OCH_3), 5.10, 5.20, and 5.26 (each 2H, s, $PhCH_2$), 6.75 (1H, s, C_8-H), 6.92 (1H, d, J = 7.8 Hz C_5'-H), 6.94 (1H, dd, J = 7.8 Hz and J = 1.9 Hz, C_6'-H), 7.18 (1H, d, J = 1.9 Hz, C_2'-H), 7.28–7.53 (15H, m, Ar-H × 15), 7.81 (1H, s, C_2-H); Anal. Calcd. for $C_{37}H_{29}IO_6$: C, 63.80; H, 4.22; Found: C, 63.71.66; H, 4.24..

Acetal 8. ^{1}H NMR ($CDCl_3$) δ: 3.01 and 3.22 (each 3H, s, OCH_3), 4.70 and 4.72 (each 1H, d, J = 10.4 Hz, CH), 5.11, 5.16, and 5.20 (each 2H, s, $PhCH_2$), 6.56 (1H, d, J = 8.3 Hz, Ar-H), C_8-H), 6.62 (1H, dd, J = 8.3 Hz and J = 1.7 Hz, Ar-H), 6.65 (1H, d, J = 1.7 Hz, Ar-H), 6.71–7.65 (21H, m, Ar-H × 21).

The similar treatment of compound **7** (4.18 g, 5.21 mmol) with BTIB (3.06 g, 7.12 mmol) for 28 h at rt gave crude acetal **8**, which was cyclized with 20% NaOH for 40 min to give iodoisoflavone, 1.16 g (32%).

5,7,4′-Tris(benzyloxy)-6-(3-hydroxy-3-methyl-1-butynyl)-3′-methoxyisoflavone (10). Compound **9** (6.12 g, 8.79 mmol) was dissolved in DMF (25 mL) followed by the successive addition of Et_3N (100 mL), $PdCl_2$ (80 mg, 0.45 mmol), PPh_3, (220 mg, 0.82 mmol), CuI (88 mg, 0.46 mmol), and finally 2-methyl-3-butyn-2-ol (2.69 mL, 27.94 mmol). The reaction mixture was heated at 80°C under nitrogen for 2.5 h and then cooled to rt. The cool mixture was filtered through sintered glass using celite, and the filtrate was extracted with AcOEt, washed with 5% HCl and water, and dried (Na_2SO_4). The solvent was removed under reduced pressure and the resulting solid was chromatographed on silica-gel column (CH_2Cl_2: AcOEt; 9:1) and further recrystallized form AcOEt and acetone (2:1) to give compound **10** as a colorless crystalline solid, 4.24 g (74%), mp 151–153°C; ^{1}H NMR ($CDCl_3$): δ 1.51 (6H, s, CH_3 × 2), 3.91 (3H, s, OCH_3), 5.20 (6H, s, $PhCH_2$ × 3), 6.72 (1H, s, C_8-H), 6.90 (1H, d, J = 8.2 Hz C_5'-H), 6.94 (1H, dd, J = 8.2 Hz and J = 1.7 Hz, C_6'-H), 7.16 (1H, d, J = 1.7 Hz, C_2'-H), 7.26–7.52 (15H, m, Ar-H × 15), 7.79 (1H, s, C_2-H); Anal. Calcd. for $C_{42}H_{36}O_7$: C, 77.28; H, 5.56; Found: C, 77.21; H, 5.42.

5,7,4′-Trihydroxy-6-(3-hydroxy-3-methyl-1-butyl)-3′-methoxyisoflavone(lupisoflavone hydrate 2). The hydrogenation accompanied by hydrogenolysis of compound **10** (2.25 g, 3.44 mmol) was carried out over 5% Pd/C (150 mg) in a mixture of methanol (80 mL) and dioxane (80 mL) until the uptake of hydrogen ceased. The resulting compound was recrystallized from MeOH and Me_2CO to give compound **2** as a colorless solid, 1.23 g (93%), mp 220–222°C; ^{1}H NMR (Table 1). IR (KBr): ν_{max} 3443, 3083, 2966, 2870, 1665, 1519, 1464, 1208, and 1057 cm^{-1}; UV λ_{max} nm (log ε) (MeOH): 268 (4.34), 219 (4.30), (+$AlCl_3$) 268 sh (4.36), 219 (4.31), (+NaOAc) 334 (3.93), 277 (4.36), 234sh (4.24). Anal. Calcd. for $C_{21}H_{22}O_7$: C, 65.28; H, 5.74; Found: C, 65.21; H, 5.62.

7,4′-Bis(benzoyloxy)-5-hydroxy-6-(3-hydroxy-3-methylbutyl)-3′-methoxyisoflavone (11). A mixture of **2** (1.54 g, 3.98 mmol), benzoyl chloride (1.05 mL, 9.83 mmol), and K_2CO_3 (3.06 g, 22.16 mmol) in acetone (45 mL) was heated at 45°C under nitrogen for 25 min. Filtering off K_2CO_3 and removing the solvent under reduced pressure gave a residue, which was extracted with AcOEt, washed with 5% HCl and water, and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the resulting compound was recrystallized from a mixture of CH_2Cl_2 and acetone to give **11** as colorless needles, 2.03 g (86%), mp 182–183°C; ^{1}H NMR ($CDCl_3$): δ 1.21 (6H, s, CH_3 × 2), 1.74 and 2.77 (each 2H, m, CH_2), 3.85 (3H, s, OCH_3), 6.90 (1H, s, C_8-H), 7.10–7.72 (13H, m, Ar-H × 13), 8.11 (1H, s, C_2-H), OH groups were not observed due to exchange; Anal. Calcd. for $C_{35}H_{30}O_9$; C, 70.70; H, 5.09; Found: C, 70.57; H, 5.16.

7,4′-Bis(benzoyloxy)-6-(3-hydroxy-3-methylbutyl)-3′-methoxy-5-tosyloxyisoflavone (12). A mixture of **11** (1.24 g, 2.08 mmol), tosyl chloride (681 mg, 3.56 mmol), and K_2CO_3 (2.87 g, 20.8 mmol) in acetone (65 mL) was refluxed under nitrogen for 3 h. The reaction mixture was cooled to rt, neutralized with 5% aqueous HCl, extracted with AcOEt, washed with water, and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the resulting compound was recrystallized from a mixture of $CHCl_3$ and acetone to give **12** as colorless needles, 1.28 g (82%), mp 170–171°C; ^{1}H NMR ($CDCl_3$): δ 1.13 (6H, s, CH_3 × 2), 1.71 and 2.78 (each 2H, m, CH_2), 2.42 (3H, s, Ar-CH_3), 3.85 (3H, s, OCH_3), 7.10–7.82 (18H, m, Ar-H × 18), 7.93 (1H, s, C_2-H); Anal. Calcd. for $C_{42}H_{36}O_{11}S$: C, 67.37; H, 4.85; Found: C, 67.31; H, 4.93.

7,4′-Bis(benzoyloxy)-6-(3-methyl-2-butenyl)-3′-methoxy-5-tosyloxyisoflavone (13). To a solution of **12** (1.20 g, 1.60 mmol) in dry toluene (12 mL) was added p-TsOH·H_2O (2.6 mL of a 5.24 × $10^{-1}$$M$ solution in acetic acid). The reaction mixture was refluxed under nitrogen for 2 h. After cooling, the reaction mixture was extracted with ether, washed with 5% $NaHCO_3$ and water, and dried (Na_2SO_4). After removal of the solvent, the obtained crude was chromatographed on silica-gel column ($CHCl_3$ as eluent) to give 6-alkenylisoflavone (802 mg) as a crude solid. The ^{1}H NMR spectrum showed that it was a mixture of 6-(3-methyl-2-butenyl)isoflavone (**13**) and its regioisomer, 6-(3-methyl-3-butenyl)isolavone **13′** (**13**:**13′** = 77:23). The regioisomeric mixture was dissolved in CH_2Cl_2 (6 mL) followed by the careful addition of benzohydroxymoyl chloride (165 mg, 1.06 mmol) and Et_3N (0.3 mL, 2.13 mmol) in an ice bath. The whole reaction mixture was then stirred for rt under nitrogen for 10 h. The mixture was quenched with aqueous NH_4Cl and extracted with CH_2Cl_2, washed with water, and dried (Na_2SO_4). The resulting semisolid was chromatographed on a silica-gel column ($CHCl_3$:Me_2CO; 12:1) to give the 6-prenylisoflavone **13**, which was recrystallized from a mixture of $CHCl_3$ and acetone to

give **13** as a crystalline solid, 596 mg (51%), mp 170–172°C; ^{1}H NMR ($CDCl_3$): δ 1.39 and 1.46 (each 3H, s, CH_3 × 2), 2.39 (3H, s, CH_3), 3.35 (2H, d, J = 6.3 Hz, CH_2), 3.86 (3H, s, OCH_3), 4.95 (1H, br.t, J = 6.3 Hz, CH), 7.05–7.70 (18H, m, Ar-H × 18), 7.91 (1H, s, C_2-H); Anal. Calcd. for $C_{42}H_{34}O_{10}S$: C, 69.03; H, 4.69; Found: C, 68.21; H, 4.73.

7,4′-Bis(benzoyloxy)-5-hydroxy-6-(3-metyl-2-butenyl)-3′-methoxyisoflavone(14). Compound **13** (512 mg, 0.71 mmol) was dissolved in dry CH_2Cl_2 (15 mL), followed by the addition of BCl_3 (0.72 mL, 1*M* solution in CH_2Cl_2), in an ice bath. The reaction mixture was stirred between 20 and 25°C under nitrogen for 3 h. The resulting mixture was quenched with saturated NH_4Cl solution, extracted with CH_2Cl_2, washed with water, and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the obtained solid was purified on a silica-gel column ($CHCl_3$ as a solvent) and further recrystallized form a mixture of AcOEt and MeOH to give **14** as a colorless crystalline solid, 379 mg (94%), mp 153–155°C; ^{1}H NMR ($CDCl_3$): δ 1.55 and 1.60 (each 3H, s, CH_3 × 2), 3.38 (2H, d, J = 6.6 Hz, CH_2), 3.88 (3H, s, OCH_3), 5.17 (1H, br.t, J = 6.6 Hz, CH), 6.88 (1H, s, C_8-H), 7.10–7.70 (13H, m, Ar-H × 13), 8.02 (1H, s, C_2-H), 13.13 (1H, s, C_5-OH); Anal. Calcd. for $C_{35}H_{38}O_8S$: C, 72.91; H, 4.89; Found: C, 72.87; H, 4.81.

5,7,4′-Trihydroxy-6-(3-metyl-2-butenyl)-3′-methoxyisoflavone (lupisoflavone) (1). Compound **14** (320 mg, 0.56 mmol) was dissolved in a mixture of methanol (5 mL) and dioxane (5 mL) followed by the addition of 10% NaOH (3.0 mL, 7.5 mmol). The reaction mixture was stirred at 25°C for 30 min. The resulting mixture was neutralized with 2% HCl and the organic layer was evaporated under reduced pressure. The obtained residue was extracted with AcOEt, washed with water, and dried (Na_2SO_4). The solvent was removed under reduced pressure to give a solid mass, which was chromatographed on silica-gel column (AcOEt:$CHCl_3$; 1:6) and the resulting compound was recrystallized from a mixture of chloroform and ethyl acetate to give the 6-prenylisoflavone **1** as pale yellow needles, 126 mg (62%), mp 161–163°C; ^{1}H NMR (Table 1); IR (KBr) ν_{max}: 3435, 3085, 2949, 2865, 1649, 1517, 1460, 1205, and 1068 cm^{-1}; UV λ_{max} nm (log ε) (MeOH): 267sh (4.39), 220 (4.36), (+$AlCl_3$) 341 (3.97), 274sh (4.39), (+NaOAc) 338 (4.12), 267sh (4.46); Anal. Calcd. for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47; Found: C, 68.39; H, 5.31.

5,7,4′-Triacetoxy-6-(3-metyl-2-butenyl)-3′-methoxyisoflavone (15). Acetylation of **1** (50 mg, 0.13 mmol) was achieved by the acetic anhydride–pyridine method at 110°C for 2 h. The obtained gammy mass was chromatographed on a silica-gel column ($CHCl_3$:hexane; 5:1) to give colorless needles, 54 mg (80%), mp 154–156°C; ^{1}H NMR ($CDCl_3$): δ 1.67 and 1.75 (each 3H, s, CH_3 × 2), 2.34, 2.36, and 243 (each 3H, s, $COCH_3$), 3.32 (2H, br. d, CH_2), 3.86 (3H, s, OCH_3), 5.12 (1H, br. t, CH), 6.98 (1H, dd, J = 8.3 Hz, J = 1.7 Hz, $C_{6'}$-H), 7.08 (1H, d, J = 1.7 Hz, $C_{2'}$-H), 7.24 (1H, s, C_8-H), 7.85 (1H, s, C_2-H); Anal. Calcd. for $C_{27}H_{26}O_9$: C, 65.68; H, 5.25; Found: C, 65.91; H, 5.12.

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