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A Convenient Synthesis of Prenylated Isoflavones: Synthesis of Licoricone and Related Compounds[1)]

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The condensation of 6′,7-bis(benzoyloxy)-2′,4′-dimethoxyisoflavone (**18**) with 2-methyl-3-buten-2-ol, followed by hydrolysis of the resultant 6′, 7-bis(benzoyloxy)-2′,4′-dimethoxy-3′-(3-methyl-2-butenyl)isoflavone (**19**) gave 6′,7-dihydroxy-2′,4′-dimethoxy-3′-(3-methyl-2-butenyl)-isoflavone (licoricone) (**1**). Its isomer, 6′,7-dihydroxy-2′,4′-dimethoxy-5′-(3-methyl-2-butenyl)-isoflavone (**2**), was also synthesized from 7-benzoyloxy-6′-hydroxy- or 6′,7-bis(benzoyloxy)-2′,4′-dimethoxy-5′-(3-methyl-2-butenyl)isoflavone (**11** or **20**).

Keywords——isoflavone; selective prenylation (3-methyl-2-butenylation); prenylated isoflavone; 6′,7-dihydroxy-2′,4′-dimethoxy-3′-(3-methyl-2-butenyl)isoflavone (licoricone); 6′,7-dihydroxy-2′,4′-dimethoxy-5′-(3-methyl-2-butenyl)isoflavone; 6-hydroxy-2,4-dimethoxybenzaldehyde

The discovery that some prenylated (3-methyl-2-butenyl-substituted)isoflavones show considerable antifungal activity[3,4)] has aroused a renewed interest in the synthesis of prenylated isoflavones. The development of these isoflavones with antifungal activity depends on the availability of more efficient and convenient synthetic methods.

As a part of our studies on the synthesis of isoflavones prenylated on the B ring,[5)] we investigated the synthesis of licoricone, which has been isolated from the root *Glycyrrhiza uralensis* FISCHER. *et* DC. The structure of licoricone has been shown to be 6′,7-dihydroxy-2′,4′-dimethoxy-3′-(3-methyl-2-butenyl)isoflavone (**1**) on the basis of chemical and spectroscopic studies, and was finally determined by an X-ray crystallographic analysis of licoricone monobromoacetate.[6)] Licoricone is the first naturally occurring prenylated isoflavone having the trioxygenated phloroglucinol pattern on the B ring. The present paper reports in more detail the unambiguous synthesis of this natural prenylated isoflavone (licoricone) (**1**) and its isomer, 6′,7-dihydroxy-2′,4′-dimethoxy-5′-(3-methyl-2-butenyl)isoflavone (**2**).

The formylation of phloroglucinol by using *N*,*N*-dimethylformamide-phosphoryl chloride in anhydrous acetonitrile at 30—35 °C, followed by methylation of the resultant compound with iodomethane in anhydrous acetone under reflux afforded 6-hydroxy-2,4-dimethoxybenzaldehyde (**3**) in high yield based on phloroglucinol. This synthesis of **3** is more convenient than that described already.[7)] Compound **3** was converted into 6-benzyloxy-2,4-dimethoxybenzaldehyde (**4**). The condensation of **4** with 4-benzyloxy-2-hydroxyacetophenone (**5**) afforded the chalcone derivative (**6**) and the acetylation of **6** led to the acetate derivative (**7**). The oxidative rearrangement of **7** with thallium (III) nitrate trihydrate in a large amount of methanol, followed by cyclization of the resultant compound by treatment with dilute hydrochloric acid[5,8)] afforded the corresponding isoflavone (**8**). The hydrogenolysis of **8** with 10% palladium on charcoal in methanol–ethyl acetate gave the 6′,7-

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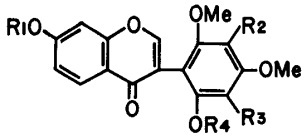
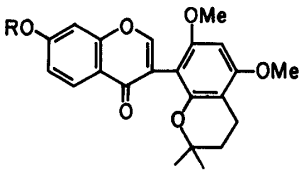
dihydroxyisoflavone (**9**), which was partially benzoylated with benzoyl chloride in pyridine to give 7-benzoyloxy-6′-hydroxyisoflavone (**10**). The condensation of **10** with 2-methyl-3-buten-2-ol in the presence of boron trifluoride etherate in anhydrous dioxane afforded 5′-(3-methyl-2-butenyl)isoflavone (**11**) and 3′,5′-bis(3-methyl-2-butenyl)isoflavone (**12**), which was converted into 6′,7-dihydroxy-2′,4′-dimethoxy-3′,5′-bis(3-methyl-2-butenyl)isoflavone (**13**). The nuclear magnetic resonance (NMR) spectrum of **11** showed the presence of two methyl groups as a singlet at δ 1.63 and 1.71, one methylene group as a doublet ($J=7$ Hz) centering at δ 3.22, and one methine proton as a triplet ($J=7$ Hz) centering at δ 5.17. Compound **11** was hydrolyzed with dilute alkali in a nitrogen atmosphere to give 6′,7-dihydroxy-2′,4′-dimethoxy-5′-(3-methyl-2-butenyl)isoflavone (**2**). The infrared (IR), ultraviolet (UV), and NMR spectra of **2** were not consistent with those of licoricone.





14: R=H
15: R=CH_3CO

1: $R_1=R_3=R_4=H$, $R_2=(CH_3)_2C=CHCH_2$
2: $R_1=R_2=R_4=H$, $R_3=(CH_3)_2C=CHCH_2$
8: $R_1=R_4=PhCH_2$, $R_2=R_3=H$
9: $R_1=R_2=R_3=R_4=H$
10: $R_1=PhCO$, $R_2=R_3=R_4=H$
11: $R_1=PhCO$, $R_2=R_4=H$, $R_3=(CH_3)_2C=CHCH_2$
12: $R_1=PhCO$, $R_2=R_3=(CH_3)_2C=CHCH_2$, $R_4=H$
13: $R_1=R_4=H$, $R_2=R_3=(CH_3)_2C=CHCH_2$
16: $R_1=R_4=CH_3CO$, $R_2=H$, $R_3=(CH_3)_2C=CHCH_2$
17: $R_1=R_4=CH_3$, $R_2=H$, $R_3=(CH_3)_2C=CHCH_2$
18: $R_1=R_4=PhCO$, $R_2=R_3=H$
19: $R_1=R_4=PhCO$, $R_2=(CH_3)_2C=CHCH_2$, $R_3=H$
20: $R_1=R_4=PhCO$, $R_2=H$, $R_3=(CH_3)_2C=CHCH_2$
21: $R_1=R_4=CH_3CO$, $R_2=(CH_3)_2C=CHCH_2$, $R_3=H$

Compound **2** was cyclized with a small amount of conc. hydrochloric acid in methanol to give the chroman derivative (**14**), which was converted into the acetate (**15**). Furthermore, compound **2** was converted into the diacetate (**16**) and the dimethyl ether (**17**). On the basis of these results, the isoflavone **2** was shown to be an isomer of licoricone.

The exhaustive benzoylation of **9** with benzoyl chloride in pyridine at 62—63 °C, followed by condensation of the resultant compound (**18**) with 2-methyl-3-buten-2-ol afforded a mixture of two isomeric compounds, 6′,7-bis(benzoyloxy)-2′,4′-dimethoxy-3′-(3-methyl-2-butenyl)isoflavone (**19**) and its positional isomer (**20**), which was converted into **2**. The NMR spectrum of **19** showed the presence of one 3-methyl-2-butenyl group and four aromatic protons. The hydrolysis of **19** with dilute alkali afforded the desired isoflavone (**1**). The cyclization of **1** was not induced by treatment with conc. hydrochloric acid in methanol. Compound **1** was subsequently converted into the diacetate (**21**). The melting points of compounds **1** and **21** were depressed by admixture with **2** and **16**, respectively. The IR, UV, and NMR spectral data for the synthetic isoflavone **1** and the diacetate **21** were shown to be identical with those of natural licoricone and its diacetate, respectively.

On the basis of these results, the structure of licoricone was confirmed to be 6′,7-dihydroxy-2′,4′-dimethoxy-3′-(3-methyl-2-butenyl)isoflavone (**1**).

Experimental

Melting points are uncorrected. The IR spectra were taken on a Hitachi 260-10 spectrophotometer, and the UV spectra on a Hitachi 124 spectrophotometer. The ^{1}H-NMR spectra were measured with Hitachi R-20 spectrometer (60 MHz), using tetramethylsilane as an internal standard (δ, ppm). Column chromatography and thin-layer

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chromatography (TLC) were carried out on Kieselgel 60 (70—230 mesh) and with Kieselgel 60 F-254 (Merck).

6-Hydroxy-2,4-dimethoxybenzaldehyde (3)——After the gradual addition of phosphoryl chloride (14.6 g) to *N*,*N*-dimethylformamide (DMF, 7 g) with stirring below 10 °C, anhydrous phloroglucinol (10 g) in anhydrous acetonitrile (140 ml) was added dropwise to the mixture at 10—15 °C. The reaction mixture was further stirred at 30—35 °C for 3 h, then neutralized with saturated sodium acetate, extracted with ethyl acetate, washed with water, and dried with sodium sulfate. The solvent was removed under reduced pressure, and to the residue was added a mixture of dichloromethane (150 ml) and petroleum ether (150 ml) to give precipitates. The precipitates were collected by filtration and washed with petroleum ether to give orange crystals (12.1 g), which were a mixture of two compounds. The crude mixture was refluxed with iodomethane (30.1 g) in the presence of potassium carbonate (33 g) in acetone (200 ml) with stirring for 3 h. After the removal of potassium carbonate and the solvent, the residue was extracted with ethyl acetate. The extract was washed with dil. hydrochloric acid and water, and dried with sodium sulfate. The solvent was removed, and then the residue chromatographed over a silica gel column with chloroform to give a main product ($Rf=0.73$) as the first fraction. The compound was crystallized from petroleum ether to give **3** (8.8 g, 60% based on phloroglucinol) as colorless needles, mp 67—68 °C. IR (KBr): 3450, 1640 cm^{-1}. NMR($CDCl_3$) δ: 3.80 and 3.82 (each s, 3H, OCH_3), 5.87 and 5.98 (each d, 1H, $J=2$ Hz, arom-H), 10.04 (s, 1H, CHO), 12.44 (s, 1H, OH). *Anal.* Calcd for $C_9H_{10}O_4$: C, 59.33; H, 5.53. Found: C, 59.34; H, 5.70.

6-Benzyloxy-2,4-dimethoxybenzaldehyde (4)——A mixture of **3** (3.86 g), benzyl chloride (2.3 ml), DMF (15 ml), and potassium carbonate (5.0 g) was heated with stirring at 150—153 °C for 40 min. Potassium carbonate was filtered off and the solvent was removed under reduced pressure. The residue was recrystallized from methanol to give **4** (3.63 g, 63%) as colorless needles, mp 89—91 °C. NMR($CDCl_3$) δ: 3.78 and 3.82 (each s, 3H, OCH_3), 5.10 (s, 2H, $C_6H_5C\underline{H}_2$), 6.03 and 6.11 (each d, 1H, $J=2$ Hz, arom-H), 7.20—7.49 (m, 5H, C_6H_5), 10.35 (s, 1H, CHO). *Anal.* Calcd for $C_{16}H_{16}O_4$: C, 74.36; H, 5.83. Found: C, 74.25; H, 6.15.

4-Benzyloxy-2-hydroxyacetophenone (5)——A mixture of 2,4-dihydroxyacetophenone (5 g), benzyl chloride (4.2 ml), DMF (20 ml), and potassium carbonate (7.7 g) was heated with stirring at 150—153 °C for 1 h. The reaction mixture was worked up in the same manner as in the preparation of **4**. The product was recrystallized from methanol to give **5** (5.35 g, 62%) as colorless needles, mp 94—95 °C. NMR($CDCl_3$) δ: 2.50 (s, 3H, $COCH_3$), 5.03 (s, 2H, $C_6H_5C\underline{H}_2$), 6.48 (dd, 1H, $J=2.6$, 10 Hz, C_5-H), 6.48 (d, 1H, $J=2.6$ Hz, C_3-H), 7.33 (s, 5H, C_6H_5), 7.59 (d, 1H, $J=10$ Hz, C_6-H). *Anal.* Calcd for $C_{15}H_{14}O_3$: C, 70.57; H, 5.92. Found: C, 70.44; H, 6.02.

4',6-Bis(benzyloxy)-2'-hydroxy-2,4-dimethoxychalcone (6)——A mixture of **5** (6 g) and **4** (6.2 g) was refluxed in the presence of piperidine (3.4 ml) in ethanol (95 ml) for 6 h to give yellow precipitates. The precipitates were recrystallized from ethyl acetate to give **6** (9.98 g, 88%) as yellow needles, mp 157—159 °C. NMR($CDCl_3$) δ: 3.80 and 3.86 (each s, 3H, OCH_3), 5.02 and 5.07 (each s, 2H, $C_6H_5C\underline{H}_2$), 6.09 and 6.18 (each d, 1H, $J=2$ Hz, C_3- and C_5-H), 6.19 (dd, 1H, $J=2$, 9 Hz, $C_{5'}$-H), 6.43 (d, 1H, $J=2$ Hz, $C_{3'}$-H), 7.08 (d, 1H, $J=9$ Hz, $C_{6'}$-H), 7.28—7.59 (m, 10H, $C_6H_5\times2$), 7.78 and 8.35 (each d, 1H, $J=16$ Hz, CH=), 13.79 (s, 1H, OH). *Anal.* Calcd for $C_{31}H_{28}O_6$: C, 74.98; H, 5.68. Found: C, 75.25; H, 5.96.

2'-Acetoxy-4',6-bis(benzyloxy)-2,4-dimethoxychalcone (7)——Compound **6** was converted into the acetate **7** by an acetic anhydride–sodium acetate method. Compound **7** was crystallized from ether to give pale yellow needles, mp 139—140 °C. NMR($CDCl_3$) δ: 2.23 (s, 1H, $COCH_3$), 3.77 and 3.82 (each s, 3H, OCH_3), 5.05 (s, 4H, $C_6H_5C\underline{H}_2\times2$), 6.08 and 6.17 (each d, 1H, $J=2$ Hz, C_3- and C_5-H), 6.67 (d, 1H, $J=2$ Hz, $C_{3'}$-H), 6.73 (dd, 1H, $J=2$, 8 Hz, $C_{5'}$-H), 7.49 (d, 1H, $J=8$ Hz, , $C_{6'}$-H), 7.13—7.47 (m, 10H, $C_6H_5\times2$), 7.55 and 8.55 (each d, 1H, $J=16$ Hz, CH=). *Anal.* Calcd for $C_{33}H_{30}O_7$: C, 73.59; H, 5.61. Found: C, 73.88; H, 5.43.

6',7-Bis(benzyloxy)-2',4'-dimethoxyisoflavone (8)——A mixture of **7** (4 g) and thallium (III) nitrate trihydrate (4 g) was stirred in methanol (2.6 l) at 37—39 °C for 8 h, then 10% hydrochloric acid (136 ml) was added, and the mixture was further refluxed for 3 h. The precipitates were filtered off and the filtrate was poured into ice-cold water (1.8 l). The mixture was allowed to stand overnight at room temperature to give precipitates. The precipitates were recrystallized from methanol to give **8** (3.53 g, 96%) as colorless needles, mp 100—102 °C. NMR($CDCl_3$) δ: 3.67 and 3.73 (each s, 3H, OCH_3), 4.98 and 5.08 (each s, 2H, $C_6H_5C\underline{H}_2$), 6.20 (s, 2H, $C_{3'}$- and $C_{5'}$-H), 6.83 (d, 1H, $J=2$ Hz, C_8-H), 6.99 (dd, 1H, $J=2$, 9 Hz, C_6-H), 7.20 and 7.33 (each s, 5H, C_6H_5), 7.66 (s, 1H, C_2-H), 8.17 (d, 1H, $J=9$ Hz, C_5-H). *Anal.* Calcd for $C_{31}H_{26}O_6$: C, 75.29; H, 5.30. Found: C, 75.43; H, 5.48.

6',7-Dihydroxy-2',4'-dimethoxyisoflavone (9)——Compound **8** (2.8 g) was hydrogenolyzed over 10% palladium on charcoal (500 mg) in a mixture of methanol (80 ml) and ethyl acetate (160 ml) until the uptake of hydrogen ceased. The catalyst was filtered off and the solvent was removed under reduced pressure. The residue was recrystallized from methanol to give **9** (1.3 g, 73%) as colorless needles, mp 266—268 °C. NMR(DMSO) δ: 3.60 and 3.71 (each s, 3H, OCH_3), 6.10 (s, 2H, $C_{3'}$- and $C_{5'}$-H), 6.81 (d, 1H, $J=2$ Hz, C_8-H), 6.88 (dd, 1H, $J=2$, 8 Hz, C_6-H), 7.87 (d, 1H, $J=8$ Hz, C_5-H), 7.87 (s, 1H, C_2-H), 9.78 (br, 2H, OH×2). *Anal.* Calcd for $C_{17}H_{14}O_6$: C, 64.96; H, 4.49. Found: C, 64.95; H, 4.44.

7-Benzoyloxy-6'-hydroxy-2',4'-dimethoxyisoflavone (10)——Benzoyl chloride (1.04 ml) in anhydrous ether (15 ml) was gradually added to a solution of **9** (2 g) in pyridine (40 ml) at 5 °C, and the mixture was stirred at 5—10 °C for 6 h. The reaction mixture was poured into ice-cold water, acidified with conc. hydrochloric acid, and allowed to stand overnight in a refrigerator to give precipitates. Recrystallization from dichloroethane resulted in recovery of the

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starting material **9** (1.1 g) as an insoluble substance, and concentration of the mother liquor gave **10** (1.01 g, 38%) as colorless needles, mp 215—216.5 °C. NMR($CDCl_3$) δ: 3.66 and 3.74 (each s, 3H, OCH_3), 6.05 and 6.14 (each d, 1H, $J=2$ Hz, $C_{3'}$- and $C_{5'}$-H), 7.42 (dd, 1H, $J=2$, 8 Hz, C_6-H), 7.45 (d, 1H, $J=2$ Hz, C_8-H), 7.54—8.36 (m, 5H, C_6H_5CO), 7.89 (s, 1H, C_2-H), 8.19 (d, 1H, $J=8$ Hz, C_5-H), 8.97 (s, 1H, OH). *Anal.* Calcd for $C_{24}H_{18}O_7$: C, 68.89; H, 4.34. Found: C, 68.68; H, 4.17.

7-Benzoyloxy-6′-hydroxy-2′,4′-dimethoxy-5′-(3-methyl-2-butenyl)isoflavone (11) and 7-Benzoyloxy-6′-hydroxy-2′,4′-dimethoxy-3′,5′-bis(3-methyl-2-butenyl)isoflavone (12)——A solution of 2-methyl-3-buten-2-ol (0.29 ml) in anhydrous dioxane (10 ml) was gradually added to a solution of **10** (960 mg) and boron trifluoride etherate (0.42 ml) in dioxane (70 ml) in a nitrogen atmosphere, and the mixture was heated with stirring at 54—56 °C for 6 h. The reaction mixture was poured into ice-cold water and allowed to stand overnight in a refrigerator to give precipitates, which were collected and extracted with ether. The extract was washed with 5% aq. sodium carbonate solution and water, and dried with sodium sulfate. After the removal of the solvent, the residue was chromatographed over a silica gel column with dichloroethane–acetone (20 : 1) to give two main products ($Rf=0.90$ and 0.79). The compound of $Rf=0.79$ was recrystallized from aq. methanol to give **11** (205 mg, 21%) as colorless needles, mp 164—166 °C. NMR(DMSO) δ: 1.63 and 1.71 (each s, 3H, CH_3), 3.22 (d, 2H, $J=7$ Hz, CH_2), 3.64 and 3.82 (each s, 3H, OCH_3), 5.17 (t, 1H, $J=7$ Hz, CH=), 6.37 (s, 1H, $C_{3'}$-H), 7.35 (d, 1H, $J=2$ Hz, C_8-H), 7.57 (dd, 1H, $J=2$, 9 Hz, C_6-H), 7.64—8.35 (m, 5H, C_6H_5CO), 8.10 (s, 1H, C_2-H), 8.20 (d, 1H, $J=9$ Hz, C_5-H). *Anal.* Calcd for $C_{29}H_{26}O_9$: C, 71.59; H, 5.39. Found: C, 71.79; H, 5.22.

The compound of $Rf=0.90$ was a viscous pale yellow oil (**12**) (250 mg, 20%), which did not crystallize. NMR($CDCl_3$) δ: 1.69 and 1.77 (each s, 6H, $CH_3\times2$), 3.37 (d, 4H, $J=7$ Hz, $CH_2\times2$), 3.37 and 3.72 (each s, 3H, OCH_3), 5.22 (t, 2H, $J=7$ Hz, CH= $\times2$), 7.32—8.21 (m, 7H, C_6H_5CO and arom-H $\times2$), 8.26 (s, 1H, C_2-H), 8.37 (d, 1H, $J=8$ Hz, C_5-H).

6′,7-Dihydroxy-2′,4′-dimethoxy-3′,5′-bis(3-methyl-2-butenyl)isoflavone (13)——Compound **12** (235 mg) was hydrolyzed with 4% aq. sodium hydroxide solution (2.5 ml) in methanol (50 ml) in a nitrogen atmosphere at 50 °C for 1 h. The reaction mixture was acidified with dil. hydrochloric acid and extracted with ethyl acetate. The extract was washed with aq. sodium hydrogen carbonate and water, and dried with sodium sulfate. After the removal of the solvent, the residue was chromatographed over a silica gel column with chloroform–acetone (8 : 1) and the product was recrystallized from aq. methanol to give **13** (58 mg, 30%) as colorless needles, mp 200—202 °C. NMR(DMSO)δ: 1.64 and 1.72 (each s, 6H, $CH_3\times2$), 3.25 (d, 4H, $J=7$ Hz, $CH_2\times2$), 3.38 and 3.65 (each s, 3H, OCH_3), 5.18 (t, 2H, $J=7$ Hz, CH= $\times2$), 6.89 (d, 1H, $J=2$ Hz, C_8-H), 6.94 (dd, 1H, $J=2$, 8 Hz, C_6-H), 7.39 (d, 1H, $J=8$ Hz, C_5-H), 8.08 (s, 1H, C_2-H), 8.23 and 10.80 (each br, 1H, OH). *Anal.* Calcd for $C_{27}H_{30}O_6$: C, 71.98; H, 6.71. Found: C, 71.69; H, 6.42.

6′,7-Dihydroxy-2′,4′-dimethoxy-5′-(3-methyl-2-butenyl)isoflavone (2)——Compound **11** (205 mg) was hydrolyzed with 4% aq. sodium hydroxide solution (2.5 ml) in methanol (40 ml) in a nitrogen atmosphere at 50 °C for 1.5 h. The reaction mixture was worked up in the same manner as in the preparation of **13**. The resulting compound was crystallized from a mixture of dichloromethane and petroleum ether and recrystallized from aq. methanol to give **2** (92 mg, 57%) as colorless needles, mp 239—241 °C. IR (KBr): 3420, 3190, 1610, 1570 cm^{-1}. UV λ_{max}^{EtOH} nm (log ε): 248.5 (4.34), 264 (4.20), 297 inf (4.01), 304.5 sh (3.97); $\lambda_{max}^{EtOH+NaOAc}$ (log ε): 261 (4.40), 289 sh (4.06), 341 (3.96). NMR(DMSO) δ: 1.61 and 1.68 (each s, 3H, CH_3), 3.20 (d, 2H, $J=7$ Hz, CH_2), 3.64 and 3.79 (each s, 3H, OCH_3), 5.15 (1H, t, $J=7$ Hz, CH=), 6.26 (s, 1H, $C_{3'}$-H), 6.85 (d, 1H, $J=2$ Hz, C_8-H), 6.93 (dd, 1H, $J=2$, 9 Hz, C_6-H), 7.92 (d, 1H, $J=9$ Hz, C_5-H), 7.94 (s, 1H, C_2-H), 8.20 and 10.67 (each br, 1H, OH). *Anal.* Calcd for $C_{22}H_{22}O_6$: C, 69.10; H, 5.80. Found: C, 69.30; H, 5.73.

7-Hydroxy-3-(5,7-dimethoxy-2,2-dimethyl-8-chromanyl)-4*H*-chromen-4-one (14)——A mixture of **2** (50 mg) and conc. hydrochloric acid (2 ml) was refluxed in methanol (50 ml) for 4 h. The reaction mixture was poured into water to give precipitates, which were recrystallized from aq. methanol to give **14** (32 mg, 64%) as colorless needles, mp 243—245 °C. NMR(DMSO) δ: 1.13 (s, 6H, $CH_3\times2$), 1.67 and 2.52 (each chroman moiety t, 2H, $J=7$ Hz, CH_2), 3.66 and 3.82 (each s, 3H, OCH_3), 6.26 (chroman moiety s, 1H, arom-H), 6.82 (d, 1H, $J=2$ Hz, C_8-H), 6.90 (dd, 1H, $J=2$, 8 Hz, C_6-H), 7.80 (s, 1H, C_2-H), 7.89 (d, 1H, $J=8$ Hz, C_5-H), 10.57 (br, 1H, OH). *Anal.* Calcd for $C_{22}H_{22}O_6$: C, 69.10; H, 5.80. Found: C, 68.96; H, 5.76.

7-Acetoxy-3-(5,7-dimethoxy-2,2-dimethyl-8-chromanyl)-4*H*-chromen-4-one (15)——Compound **14** was converted into the acetate **15** by an acetic anhydride–sodium acetate method. Compound **15** was recrystallized from methanol to give colorless needles, mp 228.5—229 °C. UV λ_{max}^{EtOH} nm (log ε): 256 sh (4.21), 292 (3.82), 301.5 inf (3.79). NMR($CDCl_3$) δ: 1.21 (s, 6H, $CH_3\times2$), 1.71 and 2.60 (each chroman moiety t, 2H, $J=7$ Hz, CH_2), 2.33 (s, 3H, $COCH_3$), 3.70 and 3.82 (each s, 3H, OCH_3), 6.11 (chroman moiety s, 1H, arom-H), 7.09 (dd, 1H, $J=2$, 8 Hz, C_6-H), 7.20 (d, 1H, $J=2$ Hz, C_8-H), 7.70 (s, 1H, C_2-H), 8.25 (d, 1H, $J=8$ Hz, C_5-H). *Anal.* Calcd for $C_{24}H_{24}O_7$: C, 67.91; H, 5.70. Found: C, 67.68; H, 5.63.

6′,7-Diacetoxy-2′,4′-dimethoxy-5′-(3-methyl-2-butenyl)isoflavone (16)——Compound **2** was converted into the diacetate **16** by an acetic anhydride–sodium acetate method. Compound **16** was recrystallized from methanol to give colorless needles, mp 180.5—181 °C. IR (KBr): 1770, 1755, 1660, 1615, 1580 cm^{-1}. UV λ_{max}^{EtOH} nm (log ε): 256 inf (4.16), 282.5 (4.03), 301.5 sh (3.87). NMR($CDCl_3$) δ: 1.65 and 1.70 (each s, 3H, CH_3), 2.03 and 2.34 (each s, 3H,

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$COCH_3$), 3.18 (d, 2H, $J=7$ Hz, CH_2), 3.72 and 3.84 (each s, 3H, OCH_3), 5.08 (t, 1H, $J=7$ Hz, , CH=), 6.41 (s, 1H, $C_{3'}$-H), 7.08 (dd, 1H, $J=2$, 9 Hz, C_6-H), 7.22 (d, 1H, $J=2$ Hz, C_8-H), 7.71 (s, 1H, C_2-H), 8.23 (d, 1H, $J=9$ Hz, C_5-H). *Anal.* Calcd for $C_{26}H_{26}O_8$: C, 66.95; H, 5.58. Found C, 66.82; H, 5.38.

2′,4′,6′,7-Tetramethoxy-3′-(3-methyl-2-butenyl)isoflavone (17)——A mixture of **2** (90 mg), dimethyl sulfate (0.67 ml), and potassium carbonate (0.88 g) was refluxed in anhydrous acetone (45 ml) for 6 h. Water (70 ml) was added to the reaction mixture, and acetone was removed by heating. The residue was extracted with ether, washed with water, and dried with sodium sulfate. The resulting compound was recrystallized from methanol to give **17** (45 mg, 47%) as colorless needles, mp 134—135 °C. IR (KBr): 1640, 1630, 1615, 1585, 1570 cm^{-1}. UV λ_{max}^{EtOH} nm (log ε): 247 (4.41), 283.5 (4.12), 293.5 sh (4.08), 303.5 (4.03). NMR($CDCl_3$) δ: 1.68 and 1.76 (each s, 3H, CH_3), 3.30 (d, 2H, $J=7$ Hz, CH_2), 3.46, 3.72, 3.84, and 3.88 (each s, 3H, OCH_3), 5.18 (t, 1H, $J=7$ Hz, CH=), 6.33 (s, 1H, $C_{5'}$-H), 6.81 (d, 1H, $J=2$ Hz, C_8-H), 6.90 (dd, 1H, $J=2$, 9 Hz, C_6-H), 7.72 (s, 1H, C_2-H), 8.16 (d, 1H, $J=9$ Hz, C_5-H). *Anal.* Calcd for $C_{24}H_{26}O_6$: C, 70.23; H, 6.39. Found: C, 70.11; H, 6.15.

6′,7-Bis(benzoyloxy)-2′,4′-dimethoxyisoflavone (18)——Benzoyl chloride (1.33 ml) was added to a solution of **9** (1.2 g) in pyridine (40 ml) and the whole was stirred at 62—64 °C for 5 h. The reaction mixture was poured into ice-cold water, acidified with conc. hydrochloric acid, and allowed to stand overnight in a refrigerator to give precipitates. The precipitates were recrystallized from chloroform–petroleum ether to give **18** (1.8 g, 90%) as colorless plates, mp 229—230 °C. NMR($CDCl_3$) δ: 3.76 and 3.82 (each s, 3H, OCH_3), 6.49 (s, 2H, $C_{3'}$- and $C_{5'}$-H), 7.22—8.41 (m, 13H, $C_6H_5CO\times2$ and arom-H×3), 7.84 (s, 1H, C_2-H). *Anal.* Calcd for $C_{31}H_{22}O_8$: C, 71.26; H, 4.24. Found: C, 71.15; H, 4.15.

6′,7-Bis(benzoyloxy)-2′,4′-dimethoxy-3′-(3-methyl-2-butenyl)isoflavone (19) and 6′,7-Bis(benzoyloxy)-2′,4′-dimethoxy-5′-(3-methyl-2-butenyl)isoflavone (20)——A solution of 2-methyl-3-buten-2-ol (0.43 ml) in dioxane (20 ml) was added to a solution of **18** (1.81 g) and boron trifluoride etherate (0.64 ml) in dioxane (130 ml) in a nitrogen atmosphere, and the mixture was stirred at 59—61 °C for 15 h. The reaction mixture was poured into ice-cold water, extracted with ether, and allowed to stand at room temperature for 5—6 h to give precipitates. The precipitates, collected by filtration, consisted of the starting material **18**. The mother liquor was chromatographed over a silica gel column with dichloroethane–acetone–hexane (20 : 1 : 4) to give two products ($Rf=0.67$ and 0.49) and the starting material ($Rf=0.40$). The pale yellow viscous oil obtained from the first fraction ($Rf=0.67$) was crystallized from aq. methanol to give **19** (243 mg, 12%) as pale yellow needles, mp 136—138 °C. UV λ_{max}^{EtOH} nm (log ε): 283.5 inf (3.98), 293 sh (3.90), 302.5 sh (3.86). NMR ($CDCl_3$) δ: 1.71 and 1.79 (each s, 3H, CH_3), 3.41 (s, 2H, $J=7$ Hz, CH_2), 3.53 and 3.84 (each s, 3H, OCH_3), 5.26 (t, 1H, $J=7$ Hz, CH=), 6.68 (s, 1H, $C_{5'}$-H), 7.14—8.44 (m, 13H, $C_6H_5\times2$ and arom-H×3), 7.93 (s, 1H, C_2-H). *Anal.* Calcd for $C_{36}H_{30}O_8$: C, 73.21; H, 5.21. Found: C, 73.03; H, 5.02.

The compound of $Rf=0.49$ was crystallized from aq. methanol to give **20** (621 mg, 30%) as colorless prisms, mp 182—184 °C. NMR($CDCl_3$) δ: 1.44 and 1.54 (each s, 3H, CH_3), 3.24 (d, 2H, $J=7$ Hz, CH_2), 3.76 and 3.87 (each s, 3H, OCH_3), 5.13 (t, 1H, $J=7$ Hz, CH=), 6.43 (s, 1H, $C_{3'}$-H), 7.11—8.41 (m, 13H, $C_6H_5\times2$ and arom-H×3), 7.82 (s, 1H, C_2-H). *Anal.* Calcd for $C_{36}H_{30}O_8$: C, 73.21; H, 5.12. Found: C, 73.21; H, 5.18.

Compound **20** was hydrolyzed with 4% aq. sodium hydroxide solution to give compound **2** (mp 239—240.5 °C). The melting point of **2** obtained here was not depressed by admixture with **2** synthesized above.

The starting material **18** (712 mg, 39%) was recovered in this reaction.

6′,7-Dihydroxy-2′,4′-dimethoxy-3′-(3-methyl-2-butenyl)isoflavone (Licoricone) (1)——Compound **19** (242 mg) was hydrolyzed with 4% aq. sodium hydroxide solution (3 ml) in methanol (70 ml) in a nitrogen atmosphere at 55 °C for 2 h. The reaction mixture was worked up in the same manner as in the preparation of **13**. The resulting compound was recrystallized from aq. methanol to give the desired isoflavone **1** (80 mg, 51%) as colorless needles, mp 233—235 °C (lit.[5] mp 250—251 °C). IR (KBr): 3500, 3170, 1630, 1615, 1590, 1570 cm^{-1}. UV λ_{max}^{EtOH} nm (log ε): 240 (4.39), 248 (4.38), 285 (4.11), 304.5 inf (4.04); $\lambda_{max}^{EtOH+NaOAc}$: 249.5 (4.38), 255.5 sh (4.37), 306.5 inf (3.95), 337.5 (3.93). NMR(DMSO) δ: 1.64 and 1.70 (each s, 3H, CH_3), 3.19 (d, 2H, $J=7$ Hz, CH_2), 3.39 and 3.74 (each s, 3H, OCH_3), 5.12 (t, 1H, $J=7$ Hz, CH=), 6.33 (s, 1H, $C_{5'}$-H), 6.87 (d, 1H, $J=2$ Hz, C_8-H), 6.93 (dd, 1H, $J=2$, 9 Hz, C_6-H), 7.91 (d, 1H, $J=9$ Hz, C_5-H), 8.00 (s, 1H, C_2-H), 9.67 (br, 2H, OH×2). *Anal.* Calcd for $C_{22}H_{22}O_6$: C, 69.10; H, 5.80. Found: C, 69.02; H, 5.66.

Compound **1** (120 mg) was converted into the dimethyl ether **17** by a dimethyl sulfate–potassium carbonate method. The resulting compound was recrystallized from methanol to give **17** (65 mg, 51%) as colorless needles, mp 134—136 °C. The melting point of **17** obtained here was not depressed by admixture with **17** synthesized above.

6′,7-Diacetoxy-2′,4′-dimethoxy-3′-(3-methyl-2-butenyl)isoflavone (21)——Compound **1** was converted into the diacetate **21** by an acetic anhydride–sodium acetate method. Compound **21** was recrystallized from aq. acetone to give colorless plates (34 mg, 56%), mp 146—147 °C (lit.[5] mp 172—173.5 °C). IR (KBr): 1765, 1650, 1615, 1575 cm^{-1}. UV λ_{max}^{EtOH} nm (log ε): 246 sh (4.41), 294 (3.86), 302 (3.86). NMR($CDCl_3$) δ: 1.67 and 1.76 (each s, 3H, CH_3), 2.05 and 2.34 (each s, 3H, $COCH_3$), 3.34 (d, 2H, $J=7$ Hz, CH_2), 3.46 and 3.79 (each s, 3H, OCH_3), 5.17 (t, 1H, $J=7$ Hz, CH=), 6.49 (s, 1H, $C_{5'}$-H), 7.12 (dd, 1H, $J=2$, 9 Hz, C_6-H), 7.26 (d, 1H, $J=2$ Hz, C_8-H), 7.84 (s, 1H, C_2-H), 8.28 (d, 1H, $J=9$ Hz, C_5-H). *Anal.* Calcd for $C_{26}H_{26}O_8$: C, 66.95; H, 5.58. Found: C, 66.87; H, 5.45.

On the basis of these results, the properties of this synthetically prenylated isoflavone **1** and its diacetate **21** were fully consistent with those of natural licoricone and its diacetate, respectively.

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