Synthesis of 7,2′-Dihydroxy-4′,5′-Dimethoxyisoflavanone, a Phytoestrogen with Derma Papilla Cell Proliferative Activity

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Abstract: This paper reports a concise and scalable method for the synthesis of the phytoestrogen 7,2′-dihydroxy-4′,5′-dimethoxyisoflavanone (1) via an optimized synthetic route. Compound 1 was readily obtained in 11 steps and 11% overall yield on a gram scale from commercially available 3,4-dimethoxyphenol. The key features of the synthesis include the construction of the deoxybenzoin unit through a sequence of Claisen rearrangement, oxidative cleavage, and aryllithium addition and the efficient synthesis of the isoflavanone architecture from highly functionalized 2-hydroxyketone.

Keywords: phytoestrogen; isoflavanone; Dalbergia oliveri; hair growth; deoxybenzoin; total synthesis

1. Introduction

Phytoestrogens are naturally occurring dietary compounds. They are found in a wide variety of foods, including fruits, vegetables, and grains [1–4]. These plant-derived compounds and their metabolites are structurally and functionally similar to those of mammalian estrogens, such as estradiol, and thereby exhibit weak estrogenic and anti-estrogenic effects by binding to estrogen receptors (ERs) [3,5,6]. There is increasing evidence that edible phytoestrogens have numerous health benefits, including anticancer, antioxidant, anti-inflammatory, hepatoprotective, antibacterial, and antiviral activities, that are closely related to the prevention and treatment of various types of cancers, cardiovascular diseases, osteoporosis, neurological diseases, diabetes/obesity, immune system dysfunction, menopause symptoms, and skin aging conditions, such as alopecia [1–3,5,7,8]. Hence, phytoestrogens are promising non-steroidal estrogenic compounds and potential alternatives to estrogen replacement therapy (ERT) for human healthcare.

Phytoestrogens are classified into several subgroups, such as flavonoids, isoflavonoids, and lignans, based on their structural motifs and biosynthetic pathways. Furthermore, isoflavonoids vary among subclasses, such as isoflavones, isoflavonones, isoflavans, pterocarpanes, and coumestans [1,2,9,10]. Owing to their structural rarity, as well as their unique and diverse range of biological functions, the chemistry related to the isolation, structural elucidation, and bioactivities of isoflavonones, along with their therapeutic applications, has been extensively investigated [10–12].

In 2003, 7,2′-dihydroxy-4′,5′-dimethoxyisoflavanone (1) was first isolated from the heartwood of Dalbergia louvelii R. Viguier (Fabaceae), which was used as a folk medicine to treat bilharzia and malaria in Madagascar [13]. More recently, 1 and its structurally related phytochemicals possessing diverse substitution patterns and oxidation states were isolated from the bark of Dalbergia oliveri Prain, a traditional Thai medicine used for the treatment of...
chronic ulcers in Southeast Asia (Figure 1) [14]. Isoflavanone 1 exhibits potent hair growth effects on immortalized dermal papilla cells (iDPCs). In a cell proliferation assay, 1 induced significant cell proliferative activity (54.1% at 10 μM, EC₅₀ = 8.83 μM), which was more potent than that of Minoxidil (20.6% at 10 μM), a widely used medication for the prevention and treatment of hair loss [14]. Moreover, isoflavanone 1 induced the anagen phase of the hair cycle in a mouse model via subcutaneous (SC) injection [15].

Figure 1. Chemical structure of 7,2′-dihydroxy-4′,5′-dimethoxyisoflavanone (1).

In 2018, Kim et al. reported a sophisticated approach for the synthesis of 1. However, this synthetic route does not yield a large amount of isoflavanone 1, although the synthetic steps are relatively short [15]. Practically, the preparation of naturally occurring compounds in large quantities is a highly formidable task because the large-scale collection and isolation of natural products from natural sources are restricted. Therefore, we have been exploring an efficient and scalable synthetic strategy for the large-scale synthesis of 1 to identify the mechanism of its hair growth effects through in vivo animal model studies, as well as its wide range of health benefits. Herein, we report the synthesis of the natural isoflavanone 7,2′-dihydroxy-4′,5′-dimethoxyisoflavanone (1).

2. Results and Discussion

Our approach for the synthesis of phytoestrogen 7,2′-dihydroxy-4′,5′-dimethoxyisoflavanone (1), as shown in Figure 2, includes the efficient construction of an isoflavanone framework and a gram-scale synthetic pathway. Isoflavanone 1 was obtained from 2-hydroxyketone 2 via the annulation of the deoxybenzoin skeleton and the sequential deprotection of the two masked phenols in the final stage. The deoxybenzoin unit of 2 can be constructed through a sequence of aryllithium additions to arylacetaldehyde 3 and the subsequent oxidation of the resulting alcohol. It was expected that 3 could be easily prepared from commercially available 3,4-dimethoxyphenol 4 via Claisen rearrangement and the subsequent oxidative cleavage of the terminal alkene to introduce a crucial acetaldehyde side chain.

Figure 2. Retrosynthetic analysis of 7,2′-dihydroxy-4′,5′-dimethoxyisoflavanone (1).

The synthesis of 1 begins with the preparation of the key intermediate, deoxybenzoin 2, as shown in Scheme 1. The allylation of commercially available 3,4-dimethoxyphenol 4 and subsequent Claisen rearrangement in N,N-diethylaniline [16] solely produced o-allyl-substituted phenol 6, which was readily converted to benzyl ether 7. The dihydroxylation of the terminal alkene of 7 and subsequent oxidative cleavage by NaIO₄ readily afforded...
arylacetaldehyde 3. Next, the lithiation of aryl bromide 8, which was prepared from commercially available 4-bromoresorcinol, and a spontaneous nucleophilic addition to the acetaldehyde of 3 afforded benzyl alcohol 9, which was converted to methoxymethyl (MOM)-protected deoxybenzoin 10 by pyridinium dichromate (PDC) oxidation. The selective MOM deprotection of the phenol adjacent to the ketone in deoxybenzoin 10 finally afforded 2-hydroxyketone 2, which is a key intermediate for the construction of the isoflavanone framework of 1.

Using precursor 2, the isoflavanone skeleton of 1 was constructed, as shown in Scheme 2. Previously, Gouda et al. reported an efficient and scalable approach to construct the isoflavanone framework [17]. Therefore, Gouda’s protocol was employed to obtain the fully functionalized isoflavanone 11 with paraformaldehyde and Et₂NH in refluxing MeOH. As expected, isoflavanone 11 was obtained with a yield of 88% on a multi-gram scale. Finally, sequential deprotection reactions were performed for the two phenols in 11 with Bn and MOM protecting groups. However, initial attempts to remove the protecting groups of phenols were unsuccessful. In the presence of Pd/C or Pd(OH)₂ (Pearlman’s catalyst), the hydrogenolysis of the benzyl group in 11 unexpectedly yielded phenol 12 with a very low yield (<5%). Furthermore, under acidic conditions for the MOM deprotection of 12, phenol 12 was highly unstable and degradable, despite its structural simplicity. We assumed that the intrinsic structural instability of 12 was likely due to the presence of a free phenol moiety adjacent to the ketone in the 4-chromanone skeleton, leading to unexpected and inseparable messy mixtures, especially under acidic conditions. Therefore, the deprotection sequence for two masked phenols was changed, wherein the MOM ether was deprotected first, and the benzyl ether group was then cleaved under neutral conditions in the final stage via a hydrogenolysis reaction. Significantly, the careful deprotection of the MOM ether under acidic conditions afforded the desired phenol 13 without any degradation. Finally, the subsequent hydrogenolysis of the benzyl-protecting group successfully furnished the 7,2'-dihydroxy-4',5'-dimethoxyisoflavanone (1) on a gram scale. The spectral data for synthetic 1 were identical to the reported data for the natural product in all aspects [13].

Scheme 1. Preparation of key intermediate deoxybenzoin 2.
Scheme 2. Completion of 7,2′-dihydroxy-4′,5′-dimethoxyisoflavanone (1) synthesis.

3. Conclusions

A concise and scalable synthesis of phytoestrogen 7,2′-dihydroxy-4′,5′-dimethoxyisoflavanone (1) was performed successfully. The key features of the synthesis include a deoxybenzoin intermediate obtained via a sequence of Claisen rearrangement and oxidative cleavage for the installation of the acetaldehyde side chain and the subsequent nucleophilic addition of functionalized aryllithium. Moreover, the scalable synthesis of the isoflavanone framework from the functionalized 2-hydroxyketone enabled the completion of isoflavanone 1 synthesis. Further in vivo studies on the hair growth effects and the elucidation of the therapeutic potential of phytoestrogen 1 as a promising treatment for hair loss diseases, such as alopecia, are currently in progress.

4. Materials and Methods

4.1. General Information

Unless noted otherwise, all starting materials and reagents were obtained from commercial suppliers and were used without further purification. All solvents used for the routine isolation of products and chromatography were reagent grade and glass-distilled. Reaction flasks were dried at 100 °C. Air- and moisture-sensitive reactions were performed under an argon atmosphere. Flash column chromatography was performed using silica gel 60 (230–400 mesh, Merck, Darmstadt, Germany) with the indicated solvents. Thin-layer chromatography was performed using 0.25 mm silica gel plates (Merck). High-resolution mass data were recorded by JMS-700 (JEOL, Tokyo, Japan), and methanol solvent was used to measure the MS-ESI spectra. Infrared (IR) spectra were measured on a 1600 FTIR spectrometer (Perkin-Elmer, Waltham, MA, USA). 1H and 13C NMR spectra were recorded on JEOL-500 (JEOL, Tokyo, Japan) as solutions in deuteriochloroform (CDCl3) and hexadeuterodimethyl sulfoxide (DMSO-d6). The melting point (m.p.) was measured using Electrothermal IA9100. Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane and are referenced to the deuterated solvents (CHCl3 or HCD2SOCD3 for 1H NMR and CDCl3 or DMSO-d6 for 13C NMR). 1H NMR data are reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; dd, doublet of doublets; dt, doublet of triplet; ddd, doublet of doublet of doublets; ddt, doublet of doublet of triplets; bs, broad singlet; m, multiplet and/or multiple resonance), number of protons, and coupling constant in hertz (Hz).

4.2. 4-(Allyloxy)-1,2-dimethoxybenzene (5)

To a solution of 3,4-dimethoxyphenol (10.0 g, 64.9 mmol) in acetone (120 mL) were added allyl bromide (8.43 mL, 97.5 mmol) and K2CO3 (22.5 g, 162.5 mmol) at ambient temperature. The reaction mixture was heated to reflux. After stirring for 12 h, the reaction mixture was cooled to ambient temperature. The resulting mixture was quenched with
H$_2$O (200 mL) and diluted with EtOAc (100 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layer was washed with brine, dried over MgSO$_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/n-hexane = 1:10) to afford allyl ether 5 (12.2 g, 97%) as a colorless oil: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.71 (d, $J$ = 7.5 Hz, 2H), 7.38 (t, $J$ = 7.4 Hz, 2H), 7.31 (t, $J$ = 7.2 Hz, 1H), 6.71 (s, 1H), 6.57 (s, 1H), 5.97 (ddt, $J$ = 16.6, 10.3, 6.3 Hz, 1H), 5.07-5.03 (m, 4H), 3.83 (s, 3H), 3.83 (s, 3H), 3.38 (d, $J$ = 10.3 Hz, 2H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 145.8, 148.2, 143.0, 136.7, 116.3, 116.0, 114.0, 101.3, 56.7, 56.0, 34.8; FT-IR (thin film, neat) $\nu_{max}$ 3450, 1637, 1616, 1519, 1450, 1411, 1199, 1112, 997 cm$^{-1}$; HRMS (ESI+) calcd for C$_{11}$H$_{15}$O$_3$ (M + H$^+$) 195.1016, found 195.1013.

4.3. 2-Allyl-4,5-dimethoxyphenol (6)

Allyl ether 5 (12.2 g, 62.9 mmol) was dissolved in N,N-diethylaniline (250 mL) at ambient temperature. The reaction mixture was heated to 250 °C, stirred for 2 h, and cooled to ambient temperature. The solvent was removed by vacuum distillation. The crude residue was purified by flash column chromatography on silica gel (EtOAc/n-hexane = 1:4) to afford phenol 6 (10.8 g, 88%) as a colorless oil: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.60 (s, 1H), 6.44 (s, 1H), 5.97 (ddt, $J$ = 17.8, 9.8, 3.5 Hz, 1H), 5.15-5.10 (m, 3H), 3.80 (s, 3H), 3.77 (s, 3H), 3.32 (d, $J$ = 6.3 Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 148.5, 148.2, 143.0, 136.7, 116.3, 116.0, 114.0, 101.3, 56.7, 56.0, 34.8; FT-IR (thin film, neat) $\nu_{max}$ 3450, 1637, 1616, 1519, 1450, 1411, 1199, 1112, 997 cm$^{-1}$; HRMS (ESI+) calcd for C$_{11}$H$_{15}$O$_3$ (M + H$^+$) 195.1016, found 195.1012.

4.4. 1-Allyl-2-(benzlyoxy)-4,5-dimethoxybenzene (7)

To a solution of phenol 6 (10.8 g, 55.6 mmol) in acetone (110 mL) were added benzyl bromide (9.9 mL, 83.4 mmol) and K$_2$CO$_3$ (15.4 g, 111.2 mmol). The reaction mixture was heated to reflux. After stirring for 12 h, the reaction mixture was cooled to ambient temperature. The resulting mixture was quenched with H$_2$O (30 mL) and diluted with EtOAc (50 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layer was washed with brine, dried over MgSO$_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/n-hexane = 1:1) to afford benzyl ether 7 (13.9 g, 88%) as a colorless oil: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.43 (d, $J$ = 7.5 Hz, 2H), 7.38 (t, $J$ = 7.4 Hz, 2H), 7.31 (t, $J$ = 7.2 Hz, 1H), 6.71 (s, 1H), 6.57 (s, 1H), 5.97 (ddt, $J$ = 16.6, 10.3, 6.3 Hz, 1H), 5.07-5.03 (m, 4H), 3.83 (s, 3H), 3.83 (s, 3H), 3.38 (d, $J$ = 6.3 Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 150.4, 147.9, 143.5, 137.6, 128.6, 127.9, 127.4, 120.8, 115.4, 113.8, 99.9, 71.7, 56.6, 56.3, 34.0; FT-IR (thin film, neat) $\nu_{max}$ 1608, 1514, 1448, 1222, 1193, 1118, 1026 cm$^{-1}$; HRMS (ESI+) calcd for C$_{18}$H$_{22}$O$_5$Na (M + Na$^+$) 285.1485, found 285.1481.

4.5. 2-(2-(Benzlyoxy)-4,5-dimethoxyphenyl)acetaldehyde (3)

To a solution of benzyl ether 7 (13.9 g, 49.0 mmol) in THF/1-BuOH/H$_2$O (5:1:1, 70 mL) were added 4-methylmorpholine N-oxide (NMO) (6.89 g, 58.8 mmol) and OsO$_4$ (0.1 M solution in toluene, 5 mL, 0.5 mmol) at ambient temperature. After stirring for 5 h, the resulting mixture was quenched with sat. Na$_2$S$_2$O$_3$ solution (60 mL) and EtOAc (50 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine, dried over MgSO$_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc only) to afford diol S1 (13.3 g, 83%) as a white solid: m.p. 96–98 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.41-7.32 (m, 5H), 6.71 (s, 1H), 6.57 (s, 1H), 5.03 (s, 2H), 3.88-3.85 (m, 1H), 3.82 (s, 6H), 3.55 (dd, $J$ = 11.5, 3.4 Hz, 1H), 3.45 (dd, $J$ = 11.5, 5.8 Hz, 1H), 2.81 (dd, $J$ = 13.7, 5.7 Hz, 1H), 2.76 (dd, $J$ = 13.7, 7.5 Hz, 1H), 2.26 (bs, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 150.7, 148.3, 143.6, 136.8, 128.8, 128.3, 127.6, 118.0, 115.0, 99.5, 72.6, 71.9, 65.8, 56.6, 56.3, 34.1; FT-IR (thin film, neat) $\nu_{max}$ 3425, 2935, 1610, 1514, 1382, 1219, 1193, 1078 cm$^{-1}$; HRMS (ESI+) calcd for C$_{18}$H$_{22}$O$_5$Na (M + Na$^+$) 341.1359, found 341.1357.
To a solution of diol S1 (13.3 g, 41.7 mmol) in MeOH/H₂O (10:1, 55 mL) was added NaO₂ (10.7 g, 50.0 mmol) at ambient temperature. After stirring for 1 h, the reaction mixture was filtered through a pad of Celite and concentrated in vacuo. The crude residue was diluted with H₂O (100 mL) and EtOAc (100 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/n-hexane = 1:1) to afford aldehyde 3 (11.9 g, 99%) as a colorless oil: ¹H NMR (500 MHz, DMSO-d₆) δ 7.40 (d, J = 8.6 Hz, 1H), 6.85 (d, J = 2.3 Hz, 1H), 6.61 (dd, J = 8.6, 2.9 Hz, 1H), 5.22 (s, 2H), 5.13 (s, 2H), 3.51 (s, 3H), 3.46 (s, 3H); ¹³C NMR (125 MHz, DMSO-d₆) δ 157.7, 154.5, 133.3, 110.7, 105.5, 104.9, 95.2, 94.7, 56.5, 56.2; FT-IR (thin film, neat) νmax 2827, 2723, 1606, 1512, 1398, 1274, 1082, 1037, 921 cm⁻¹; HRMS (ESI+) calcd for C₁₁H₁₄O₄ (M + H⁺) 287.1278, found 287.1277.

4.6. 1-Bromo-2,4-bis(methoxymethyl)benzene (8)

To a solution of 4-bromoresorcinol (7.4 g, 25.8 mmol) in CH₂Cl₂ (100 mL) were added DIPEA (14.4 mL, 50.0 mmol) and MOMCl (10.1 mL, 50.0 mmol) at 0 °C. After stirring for 3 h at ambient temperature, the resulting mixture was quenched with H₂O (100 mL). The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic layer was washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/n-hexane = 1:1) to afford aryl bromide 8 (11.9 g, 86%) as a colorless oil: ¹H NMR (500 MHz, CDCl₃) δ 7.40 (d, J = 8.6 Hz, 1H), 6.85 (d, J = 2.3 Hz, 1H), 6.61 (dd, J = 8.6, 2.9 Hz, 1H), 5.22 (s, 2H), 5.13 (s, 2H), 3.51 (s, 3H), 3.46 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 157.7, 154.5, 133.3, 110.7, 105.5, 104.9, 95.2, 94.7, 56.5, 56.2; FT-IR (thin film, neat) νmax 1587, 1481, 1274, 1082, 1037, 921 cm⁻¹; HRMS (ESI+) calcd for C₁₁H₁₄O₄Br (M + H⁺) 277.0070, found 277.0070.

4.7. 2-(2-(Benzyloxy)-4,5-dimethoxyphenyl)-1-(2,4-bis(methoxymethyl)phenyl)ethan-1-ol (9)

To a solution of 1-bromo-2,4-bis(methoxymethyl)benzene 8 (8.2 g, 29.5 mmol) in dry THF (100 mL) was added n-BuLi (2.5 M in n-hexane, 13.2 mL, 32.4 mmol) at −78 °C. After stirring for 30 min at the same temperature, aldehyde 3 (7.4 g, 25.8 mmol) was added to this mixture and stirred for an additional 2 h. The resulting mixture was quenched with sat. NH₄Cl solution (100 mL) and diluted with EtOAc (50 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/n-hexane = 1:3) to afford alcohol 9 (8.75 g, 70%) as a colorless oil: ¹H NMR (500 MHz, CDCl₃) δ 7.43 (d, J = 6.9 Hz, 2H), 7.38 (t, J = 7.5 Hz, 2H), 7.32 (m, 1H), 7.17 (d, J = 8.0 Hz, 1H), 6.74 (d, J = 2.3 Hz, 1H), 6.63 (dd, J = 8.6, 2.3 Hz, 1H), 6.58 (s, 1H), 6.55 (s, 1H), 5.14-5.11 (m, 1H, 3H), 5.02 (s, 2H), 5.00 (d, J = 2.3 Hz, 2H), 3.81 (s, 3H), 3.75 (s, 3H), 3.45 (s, 3H), 3.38 (s, 3H), 3.10 (dd, J = 10.7, 4.6 Hz, 1H), 3.00 (dd, J = 13.8, 8.0 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 157.4, 154.9, 151.0, 148.1, 143.2, 137.3, 128.7, 128.1, 127.7, 126.7, 119.1, 115.2, 108.8, 103.2, 99.4, 94.6, 94.4, 71.6, 70.3, 56.5, 56.2, 56.1, 38.5; FT-IR (thin film, neat) νmax 3523, 2953, 1610, 1519, 1219, 1153, 1008 cm⁻¹; HRMS (ESI+) calcd for C₂₂H₃₂O₈Na (M + Na⁺) 507.1989, found 507.1990.

4.8. 2-(2-(Benzyloxy)-4,5-dimethoxyphenyl)-1-(2,4-bis(methoxymethyl)phenyl)ethan-1-one (10)

To a solution of alcohol 9 (7.4 g, 14.9 mmol) in dry CH₂Cl₂ (150 mL) was added PDC (13.2 g, 32.4 mmol) at ambient temperature. After stirring for 12 h, the reaction mixture was filtered through a pad of Celite and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (1% CH₂Cl₂ in EtOAc/n-hexane = 1:4) to afford ketone 10 (3.68 g, 51%) as a colorless oil: ¹H NMR (500 MHz, CDCl₃) δ 7.69 (d, J = 9.2 Hz, 1H), 7.28-7.25 (m, 5H), 6.79 (d, J = 2.3 Hz, 1H), 6.73 (s, 1H), 6.66 (dd, J = 8.6, 2.3 Hz, 1H), 6.56 (s, 1H), 5.18 (s, 2H), 5.17 (s, 2H), 4.97 (s, 2H), 4.24 (s, 2H), 3.82 (s, 3H), 3.81 (s, 3H) 3.47 (s, 3H), 3.41 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 198.6, 161.5, 158.0, 150.8, 148.4, 143.2, 137.4,
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132.4, 128.5, 127.8, 127.4, 123.0, 116.7, 114.9, 108.9, 102.9, 99.5, 94.6, 94.3, 71.5, 56.5, 56.3, 56.4, 56.2, 44.5; FT-IR (thin film, neat) \( \nu_{\text{max}} \): 1673, 1600, 1516, 1247, 1195, 1153, 1002 cm\(^{-1}\); HRMS (FAB+) calcd for C\(_{27}H_{30}O_8\) (M + H\(^+\)) 482.1941, found 482.1939.

4.9. 2-(Benzylxoy)-4,5-dimethoxyphenyl)-1-(2-hydroxy-4-(methoxymethyl)phenyl)ethan-1-one (2)

To a solution of ketone 10 (3.68 g, 7.62 mmol) in MeOH (100 mL) was added conc. HCl (0.1 mL) at ambient temperature. After stirring for 3 h at the same temperature, solvents were partially evaporated to 20 mL under reduced pressure. After the residue was triturated with EtOAc/n-hexane (1:10) for 30 min, the resulting precipitate was filtered and dried to afford 2-hydroxyketone 2 (2.67 g, 80%) as a white solid: m.p. 143-144 °C; \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \( \delta \) 12.39 (s, 1H), 7.95 (d, \( J = 9.8 \) Hz, 1H), 7.25-7.21 (m, 5H), 6.83 (s, 1H), 6.75 (s, 1H), 6.50-6.48 (m, 2H), 5.23 (s, 2H), 5.00 (s, 2H), 4.19 (s, 2H), 3.72 (s, 3H), 3.64 (s, 3H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 203.1, 165.2, 163.5, 150.3, 148.9, 143.5, 137.0, 132.4, 128.7, 128.1, 127.6, 115.0, 114.4, 114.2, 108.1, 103.8, 99.2, 94.0, 71.7, 56.6, 56.5, 56.2, 38.8; FT-IR (thin film, neat) \( \nu_{\text{max}} \): 2904, 2835, 1627, 1521, 1392, 1220, 1083, 989, 923 cm\(^{-1}\); HRMS (FAB+) calcd for C\(_{23}H_{26}O_7\) (M\(^+\)) 438.1679, found 438.1683.

4.10. 3-(2-(Benzylxoy)-4,5-dimethoxyphenyl)-7-(methoxymethyl)chroman-4-one (11)

To a solution of 2-hydroxyketone 2 (2.73 g, 6.23 mmol) in MeOH (100 mL) were added paraformaldehyde (561 mg, 18.8 mmol) and Et\(_2\)NH (1.93 mL, 18.8 mmol) at ambient temperature. The reaction mixture was heated to reflux. After stirring for 2 h at the same temperature, the resulting mixture was cooled to ambient temperature and concentrated in vacuo. The crude residue was diluted with H\(_2\)O (50 mL) and EtOAc (50 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine, dried over MgSO\(_4\), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/n-hexane = 1:3) to afford isoflavanone 11 (2.46 g, 88%) as a colorless oil: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.89 (d, \( J = 8.6 \) Hz, 1H), 7.33-7.24 (m, 5H), 6.68-6.66 (m, 2H), 6.59 (s, 1H), 6.58 (d, \( J = 2.3 \) Hz, 1H), 5.19 (s, 2H), 5.00 (s, 2H), 4.58 (dd, \( J = 12.0, 10.9 \) Hz, 1H), 4.44 (dd, \( J = 10.9, 5.8 \) Hz, 1H), 4.26 (dd, \( J = 12.0, 5.2 \) Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.47 (s, 3H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 191.6, 163.6, 163.2, 151.0, 149.3, 143.5, 137.0, 129.5, 128.6, 128.0, 127.5, 116.4, 115.4, 114.2, 110.9, 103.9, 99.6, 94.1, 71.7, 71.2, 56.6, 56.4, 56.2, 48.2; FT-IR (thin film, neat) \( \nu_{\text{max}} \): 1735, 1683, 1608, 1512, 1377, 1238, 1153, 1022 cm\(^{-1}\); HRMS (FAB+) calcd for C\(_{25}H_{26}O_7\) (M\(^+\)) 451.1757, found 451.1754.

4.11. 3-(2-(Benzylxoy)-4,5-dimethoxyphenyl)-7-hydroxychroman-4-one (13)

To a solution of isoflavanone 11 (2.40 g, 5.33 mmol) in MeOH (100 mL) was added conc. HCl (0.1 mL). The reaction mixture was heated at reflux. After stirring for 4 h at the same temperature, the resulting mixture was cooled to ambient temperature, and MeOH was evaporated to 20 mL under reduced pressure. After the residue was triturated with EtOAc/n-hexane (1:3) for 30 min, the resulting precipitate was filtered and dried to afford phenol 13 (1.80 g, 83%) as a white solid: m.p. 193-194 °C; \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \( \delta \) 10.51 (s, 1H), 7.64 (d, \( J = 8.6 \) Hz, 1H), 7.30 (d, \( J = 6.3 \) Hz, 2H), 7.24-7.20 (m, 3H), 6.79 (s, 1H), 6.78 (s, 1H), 6.47 (dd, \( J = 8.6, 2.3 \) Hz, 1H), 6.28 (d, \( J = 2.3 \) Hz, 1H), 5.00 (q, \( J = 11.7 \) Hz, 2H), 4.51 (t, \( J = 11.5 \) Hz, 1H), 4.33 (dd, \( J = 10.9, 5.7 \) Hz, 1H), 4.17 (dd, \( J = 12.6, 5.7 \) Hz, 1H), 3.73 (s, 3H), 3.62 (s, 3H); \(^13\)C NMR (125 MHz, DMSO-\(d_6\)) \( \delta \) 190.8, 164.8, 163.7, 151.1, 149.4, 143.4, 137.6, 129.6, 128.8, 128.2, 128.0, 116.0, 114.6, 111.1, 102.9, 100.7, 71.1, 70.6, 56.9, 56.4, 48.1; FT-IR (thin film, neat) \( \nu_{\text{max}} \): 3356, 1604, 1517, 1450, 1220, 1022 cm\(^{-1}\); HRMS (FAB+) calcd for C\(_{24}H_{22}O_6\) (M\(^+\)) 406.1416, found 406.1421.

4.12. 7,2′-Dihydroxy-4′,5′-dimethoxyisoflavanone (1)

To a solution of phenol 13 (1.75 g, 4.31 mmol) in MeOH (100 mL) was added Pd(OH)\(_2\) (100 mg) at ambient temperature. After stirring for 2 h under H\(_2\) gas (balloon), the resulting mixture was filtered through a pad of Celite and concentrated in vacuo. The residue was
purified by flash column chromatography on silica gel (CH₂Cl₂/MeOH = 10:1) to afford 7,2′-dihydroxy-4′,5′-dimethoxyisoflavanone 1 (1.12 g, 82%) as a white solid: m.p. 181-182 °C; 1H NMR (500 MHz, DMSO-d₆) δ 10.62 (bs, 1H), 9.19 (bs, 1H), 7.65 (d, J = 8.6 Hz, 1H), 6.64 (s, 1H), 6.50 (dd, J = 8.9, 2.3 Hz, 1H), 6.45 (s, 1H), 6.32 (d, J = 2.3 Hz, 1H), 4.57 (t, J = 11.5 Hz, 1H), 4.37 (dd, J = 10.9, 5.2 Hz, 1H), 4.10 (dd, J = 12.1, 5.2 Hz, 1H), 3.67 (s, 3H), 3.58 (s, 3H); 13C NMR (125 MHz, DMSO-d₆) δ 190.5, 164.4, 163.3, 149.5, 148.8, 141.5, 129.0, 115.4, 114.1, 112.7, 110.6, 102.4, 70.1, 56.5, 55.4, 47.1; FT-IR (thin film, neat) νmax 3300, 1598, 1514, 1459, 1267, 1199, 1107, 734 cm⁻¹; HRMS (FAB+) calcd for C₁₇H₁₆O₆ (M⁺) 316.0947, found 316.0947.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/molecules27196660/s1. File S1: Comparison of NMR spectra of 1 and copies of NMR spectra (1H and 13C). Refs. [13,15,18] are cited in the Supplementary Materials.

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References
1. Sirotkin, A.V.; Harrath, A.H. Phytoestrogens and their effects. Eur. J. Pharmacol. 2014, 741, 230–236. [CrossRef] [PubMed]
2. Patisaul, H.B.; Jefferson, W. The pros and cons of phytoestrogens. Front. Neuroendocrinol. 2010, 31, 400–419. [CrossRef]
3. Rietjens, I.M.; Louisse, J.; Beekmann, K. The potential health effects of dietary phytoestrogens. Br. J. Pharmacol. 2017, 174, 1263–1280. [CrossRef]
4. Schwartz, H.; Sontag, G.; Plumb, J. Inventory of phytoestrogen databases. Food Chem. 2009, 113, 736–747. [CrossRef]
5. Tham, D.M.; Gardner, C.D.; Haskell, W.L. Potential health benefits of dietary phytoestrogens: A review of the clinical, epidemiological, and mechanistic evidence. J. Clin. Endocrinol. Metab. 1998, 83, 2223–2235. [CrossRef] [PubMed]
6. Kim, S.H.; Park, M.J. Effects of phytoestrogen on sexual development. Korean J. Pediatr. 2012, 55, 265. [CrossRef] [PubMed]
7. Thornton, M.J. Estrogens and aging skin. Derm. Endocrinol. 2013, 5, 264–270. [CrossRef]
8. Kim, M.H.; Choi, Y.Y.; Lee, J.E.; Kim, K.; Yang, W.M. Topical treatment of hair loss with formononetin by modulating apoptosis. Planta Med. 2016, 82, 65–69. [CrossRef] [PubMed]
9. Michel, T.; Halabalaki, M.; Skaltsounis, A.-L. New concepts, experimental approaches, and dereplication strategies for the discovery of novel phytoestrogens from natural sources. Planta Med. 2013, 79, 514–532. [PubMed]
10. Al-Maharik, N. Isolation of naturally occurring novel isoflavonoids: An update. Nat. Prod. Rep. 2019, 36, 1156–1195. [CrossRef] [PubMed]
11. Veitch, N.C. Isoflavonoids of the Leguminosae. Nat. Prod. Rep. 2007, 24, 417–464. [CrossRef] [PubMed]
12. Emami, S.; Ghanbarimasir, Z. Recent advances of chroman-4-one derivatives: Synthetic approaches and bioactivities. Eur. J. Med. Chem. 2015, 93, 539–563. [CrossRef]
13. Beldjoudi, N.; Mambu, L.; Labaied, M.; Grellier, P.; Ramanitrahasimbola, D.; Rasanoaivo, P.; Martin, M.T.; Frappier, F. Flavonoids from Dalbergia l ouvelii and Their Antiplasmodial Activity. J. Nat. Prod. 2003, 66, 1447–1450. [CrossRef]
14. Park, S.J.; Nhiem, N.X.; Tai, B.H.; Le Tuan Anh, H.; Oh, S.H.; Sung, J.-H.; Kim, N.; Yoo, G.; Park, J.H.; Kwak, H.J. Proliferation Effects on Hair Growth of Compounds Isolated from the Bark of Dalbergia oliveri. *Nat. Prod. Commun.* 2017, 12, 1729–1730. [CrossRef]

15. Singh, D.K.; Kim, J.; Sung, J.H.; Kim, I. Total Syntheses of Biologically Active Pterocarpan, Isoflavan, and Isoflavanone from Dalbergia oliveri. *Bull. Korean Chem. Soc.* 2018, 39, 239–243. [CrossRef]

16. Kim, T.; Kwon, H.; Lee, D.-Y.; Kim, D.-J.; Jeon, Y.; Shin, H.; Kim, H.S.; Hur, J.; Lim, C.; Kim, E.-H. Concise syntheses and anti-inflammatory effects of isocorniculatolide B and corniculatolide B and C. *Bioorg. Chem.* 2021, 116, 105398. [CrossRef] [PubMed]

17. Gouda, P.; Grover, S.K. A simple synthesis of hydroxyisoflavanones. *Indian J. Chem.* 2001, 40B, 142–144.

18. Pôças, E.S.C.; Lopes, D.V.S.; da Silva, A.J.M.; Pimenta, P.H.C.; Leitão, F.B.; Netto, C.D.; Buarque, C.D.; Brito, F.V.; Costa, P.R.R.; Noël, F. Structure–activity relationship of wedelolactone analogues: Structural requirements for inhibition of Na+,K+-ATPase and binding to the central benzodiazepine receptor. *Bioorganic Med. Chemistry.* 2006, 14, 7962–7966. [CrossRef]