

Article

Synthesis of Natural Homoisoflavonoids Having Either 5,7-Dihydroxy-6-methoxy or 7-Hydroxy-5,6-dimethoxy Groups

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Academic Editor: Derek J. McPhee

Received: 14 July 2016; Accepted: 9 August 2016; Published: 13 August 2016

Abstract: Naturally occurring homoisoflavonoids containing either 5,7-dihydroxy-6-methoxy or 7-hydroxy-5,6-dimethoxy groups such as the antiangiogenic homoisoflavanone, cremastranone, were synthesized via three or four linear steps from the known 4-chromenone. This facile synthesis includes chemoselective 1,4-reduction of 4-chromenone and selective deprotection of 3-benzylidene-4-chromanone a containing C7-benzyloxy group.

Keywords: homoisoflavanone; cremastranone; 4-chromanone; 4-chromenone 1,4-reduction

1. Introduction

Recently, the antiangiogenic homoisoflavonoid cremastranone (**1**), isolated from the plants *Muscari armeniacum*, *Chionodoxa luciliae*, *Scilla natalensis*, *Merwillia plumbea*, and *Cremastra appendiculata* was synthesized for the first time by us [1–6]. Its naturally occurring congeners (**2–10**), which contain either 5,7-dihydroxy-6-methoxy or 7-hydroxy-5,6-dimethoxy groups, have been reported already as shown in Figure 1 and most of them lack common names other than eucomnalin (**9**; autumnalin) and 3,9-dihydroeucomnalin (**4**; 3,9-dihydroautumnalin). Two review articles deal with the natural origins and structures of most homoisoflavonoids [7,8], and thereafter various studies of the homoisoflavonoids have been published [9–11]. Nevertheless, there have not been synthetic efforts towards such homoisoflavonoids since the synthesis of **4** and **9** was reported in 1971 [12]. A chemical synthesis of 5,6,7-trisubstituted homoisoflavonoids has the potential to provide a general and expedient entry into a plethora of analogues potentially with interesting biological activities [13–15]. Herein we report the first synthesis of cremastranone's derivatives in three or four steps from the known 4-chromenone, involving a chemoselective 1,4-reduction and manipulation of protecting groups.

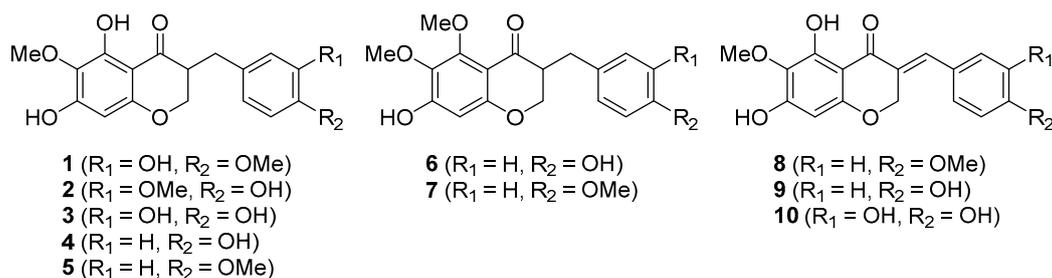
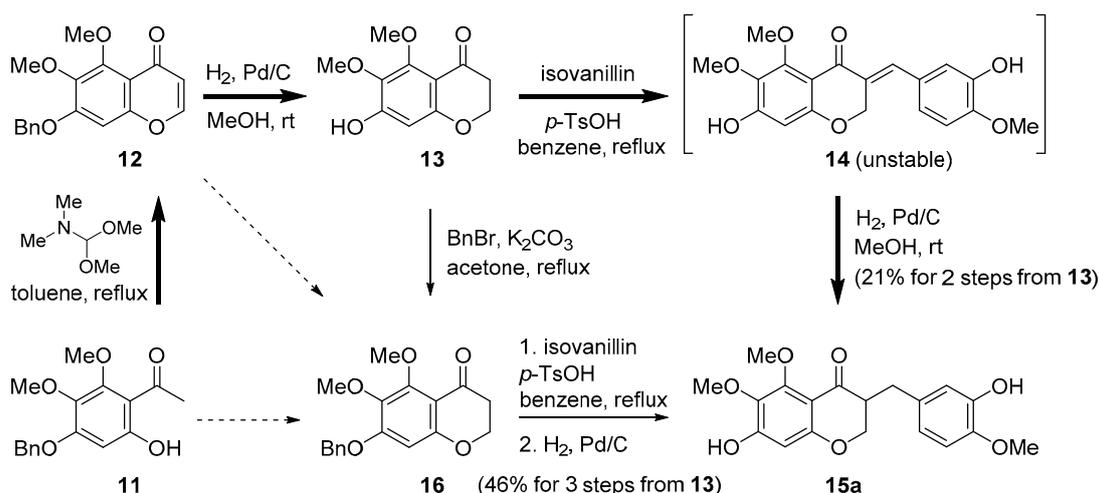


Figure 1. Naturally occurring homoisoflavonoids containing either 5,7-dihydroxy-6-methoxy (i.e., **1–5** and **8–10**) or 7-hydroxy-5,6-dimethoxy (**6** and **7**).

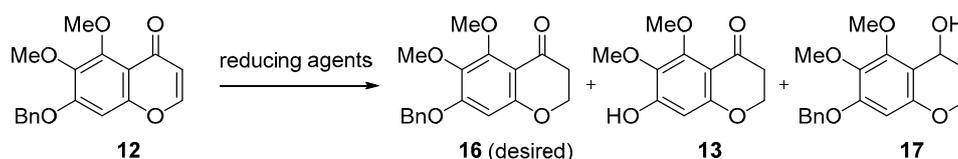
2. Results and Discussion

In our initial approach to cremastranone (**1**), the acetophenone **11** as starting material was treated with *N,N*-dimethylformamide dimethyl acetal, followed by catalytic hydrogenation to afford the 4-chromanone **13** in a good yield (Scheme 1) [14]. However, aldol condensation of **13** with isovanillin gave the unstable benzylidene products (i.e., **14a**) in a low yield; the free OH group on C7 is thought to hamper the general aldol condensation as well as the stability of the desired products. To overcome this drawback, the benzylation of the phenol group on C7 was adopted prior to aldol condensation. The aldol condensation of **16** with isovanillin afforded the desired compound **15a** in good yield.



Scheme 1. Our previous approach using 5,6,7-trisubstituted 3-benzyl-4-chromanone for the reported synthesis of cremastranone (bold arrow) [14] and the alternative pathway (normal arrow).

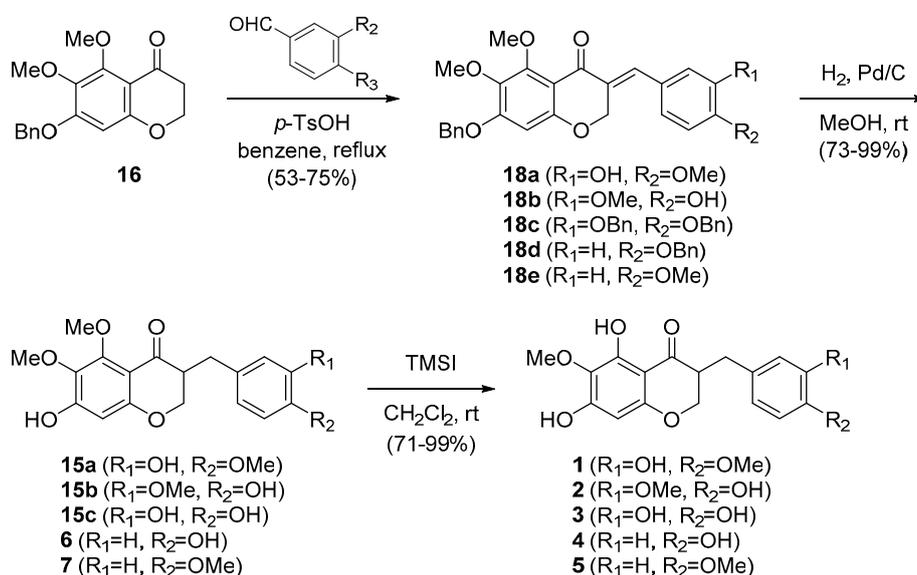
To improve chemical yield and decrease reaction steps, we focused on the direct conversion of either the acetophenone **11** or the chromenone **12** into the desired chromanone **16**. However, it was reported that the formation of a 4-chromanone from a 2-hydroxyacetophenone (i.e., **11**) is challenging [16]. The direct conversion of **12** to **16** was attempted under some reduction conditions (Table 1) [17]. Even careful catalytic hydrogenation is not likely to control a partial reduction of only the double bond. Among metal hydride reagents, the reduction using 1.5 equivalent of NaBH_4 did not proceed over 5 h, forming only a small amount of 4-chromanol **17** (<10%). Treatment with excess NaBH_4 afforded only 4-chromanol **17** in 50% yield (80% based on the recovered **12**). Diisobutylaluminum hydride (DIBAL) reduction at -60°C led to the nonselective generation of **16** (20%) and **17** (20%) in low yields. To our delight, the reduction by LiAlH_4 underwent only 1,4-addition of hydride without over-reduction quantitatively and had the advantage of being reproducible on a gram scale.

Table 1. Reduction conditions of 7-benzyloxy-5,6-dimethoxy-4-chromenone (**12**).

Entry	Condition	Yield (%) ^a		
		16	13	17
1	H ₂ , Pd/C, MeOH, rt	- ^b	99	-
2	NaBH ₄ (1.5 eq), EtOH, rt	-	-	<10
2	NaBH ₄ (2.5~5.0 eq), EtOH, rt	-	-	50
3	DIBAL ^c (1.0 eq), THF:toluene (1:1), -60 °C	20	-	20
4	LiAlH ₄ (2.0 eq), THF:Et ₂ O (1:1), -60 °C	99	-	-

^a Isolated yield; ^b not found; ^c diisobutylaluminum hydride.

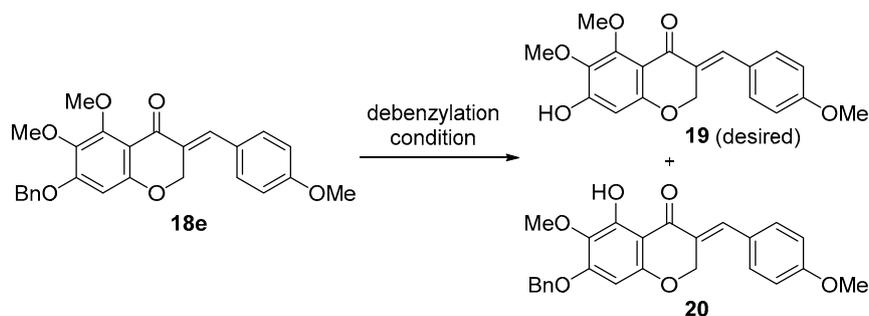
With **16** in hand, we turned to the synthesis of natural 3-benzyl-4-chromanones containing 5,7-dihydroxy-6-methoxy and 7-hydroxy-5,6-dimethoxy groups, similar to cremastranone (Scheme 2). To accomplish this, the 4-chromanone **16** was coupled with a 3,4-disubstituted benzaldehyde (i.e., vanillin or 3,4-dibenzyloxybenzaldehyde) or a 4-substituted benzaldehyde (i.e., 4-methoxybenzaldehyde or 4-benzyloxybenzaldehyde) under acidic conditions to afford 3-benzylidene-4-chromanones (**18a–18e**). Catalytic hydrogenation of **18b** and **18c**, followed by trimethylsilyl iodide (TMSI)-promoted C5-demethylation of **15b** and **15c** provided the desired **2** and **3**, respectively. In a similar manner, using catalytic hydrogenation **18d** and **18e** were transformed to **6** and **7**, which were treated with TMSI to provide **4** and **5**, respectively. The spectroscopic properties (¹H- and ¹³C-NMR, mass spectrometry) of synthetic **2**, **3**, **4** [2], **5** [5], **6** [18], and **7** [19] were compatible with those of all the natural products (see Supplementary Materials).

**Scheme 2.** Synthesis of natural products, 5,6,7-trisubstituted 3-benzyl-4-chromanones.

On the other hand, for the synthesis of three 3-benzylidene-4-chromanones (**8–10**) containing a 5,7-dihydroxy-6-methoxy group, the C7-benzyl group of the synthesized benzylidene intermediates (**18c–18e**) should be removed while keeping the C3–C9 double bond intact. With **18e** in hand, we next attempted the debenzylation on C7 as shown in Table 2. Whereas the general condition of catalytic hydrogenation under H₂ and Pd/C afforded the saturated 3-benzyl-4-chromanone such as the

synthesis of **7**, a small amount (3 mol %) of Pd/C catalyst and a short reaction time (5 min) led to the desired product **19** in moderate yield. TMSI and HBr selectively provided **19**, which was demethylated only on the C5 position. But no product formation was observed with the treatment of TiCl₄ and lithium naphthalenide. Unfortunately, the two and three benzyl groups of **18c** and **18d**, respectively, could not be cleaved simultaneously before the saturation of the C3–C9 double bond, using various conditions of catalytic hydrogenation.

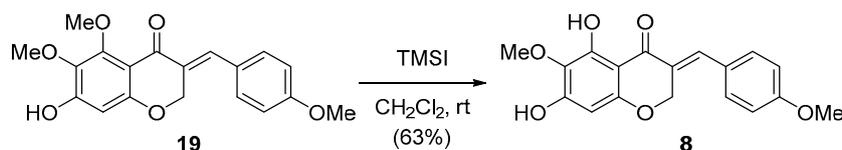
Table 2. C7-debenzylation conditions of 5,6,7-trisubstituted 3-benzylidene-4-chromanone (**18e**).



Entry	Condition	Yield (%) ^a	
		19	20
1	H ₂ , Pd/C (3 mol %), MeOH, rt	65	-
2	TMSI ^b , CH ₂ Cl ₂ , rt	-	60
3	HBr (47%), 50 °C	-	60
4	TiCl ₄ (1 eq), CH ₂ Cl ₂ , 0 °C	NR ^c	
5	Li, naphthalene, THF, -25 °C	NR	

^a Isolated yield; ^b trimethylsilyl iodide; ^c no reaction.

Finally, the debenzylated compound **19** was treated with TMSI to provide the desired **8** in good yield as shown in Scheme 3. The spectroscopic properties (¹H- and ¹³C-NMR, mass spectrometry) of synthetic **8** were compatible with those of the natural product **8** [20]. Having failed to access **9** and **10** via the debenzylation strategy, further studies on other protecting groups on C7 such as PMB (4-methoxybenzyl), MOM (methoxymethyl) and Ms (methanesulfonyl) instead of benzyl ether are under investigation.



Scheme 3. Synthesis of natural 3-benzylidene-4-chromanone **8**.

3. Materials and Methods

3.1. General Information

All starting materials and reagents were obtained from commercial suppliers and were used without further purification. Air- and moisture-sensitive reactions were performed under an argon atmosphere. Flash column chromatography was performed using silica gel 60 (230–400 mesh, Merck KGaA, Darmstadt, Germany) with the indicated solvents. Thin-layer chromatography was performed using 0.25 mm silica gel plates (Merck KGaA). ¹H- and ¹³C-NMR spectra were recorded on a Bruker 600 MHz spectrometer as solutions in deuteriochloroform (CDCl₃) or methanol-*d*₄ (Cambridge Isotope Laboratory, Andover, MA, USA). ¹H-NMR data were reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet; and/or multiple resonances), number of

protons, and coupling constant (*J*) in hertz (Hz). High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-700 (EI) (JEOL Ltd., Tokyo, Japan) and an Agilent 6530 Q-TOF LC/MS/MS system (ESI) (Agilent Technologies, Inc., Santa Clara, CA, USA).

3.2. Synthesis

7-(Benzyloxy)-5,6-dimethoxychroman-4-one (16). To a solution of the acetophenone (**11**) (100 mg, 0.33 mmol) in toluene (2.0 mL) was added *N,N*-dimethylformamide dimethyl acetal (52 μ L, 0.39 mmol). After stirring for 18 h at 80 °C, the mixture was cooled to 0 °C and *c*-HCl (0.2 mL) was added. After stirring for 1 h at 50 °C. The reaction mixture was diluted with ethyl acetate and the organic phase was washed with water and brine, and dried over anhydrous MgSO₄. The solvent was removed under reduced pressure and purified by flash column chromatography on silica gel (ethyl acetate:*n*-hexane = 1:2) to afford 7-(benzyloxy)-5,6-dimethoxy-4*H*-chromen-4-one (**12**) (101 mg, 97%). ¹H-NMR (CDCl₃, 600 MHz) δ 7.63 (d, 1H, *J* = 6.0 Hz), 7.46–7.40 (m, 4H), 7.37 (t, 1H, *J* = 6.6 Hz), 6.71 (s, 1H), 6.17 (d, 1H, *J* = 6.0 Hz), 5.20 (s, 2H), 3.97 (s, 3H), 3.92 (s, 3H); ¹³C-NMR (150 MHz, CDCl₃) δ 176.2, 156.8, 154.6, 152.9, 140.7, 135.5, 128.8, 128.4, 127.2, 114.2, 113.8, 97.6, 70.9, 62.1, 61.5, 30.9. To a stirred solution of 4-chromenone (**12**) (10 mg, 0.03 mmol) in dry THF and Et₂O (1:1) at –60 °C a solution of LiAlH₄ in dry THF was added under N₂ atmosphere. After stirring for 5 min, the reaction mixture was diluted with ethyl acetate and the organic phase was washed with water and brine, and dried over anhydrous MgSO₄. The solvent was removed under reduced pressure and purified by flash column chromatography on silica gel (ethyl acetate:*n*-hexane = 1:2) to afford the 7-(benzyloxy)-5,6-dimethoxychroman-4-one (**16**) (10 mg, 99%). ¹H-NMR (CDCl₃, 600 MHz) δ 7.43–7.37 (m, 4H), 7.35–7.33 (m, 1H), 6.29 (s, 1H), 5.13 (s, 1H), 4.42 (t, 2H, *J* = 6.0 Hz), 3.92 (s, 3H), 3.82 (s, 3H), 2.71 (t, 2H, *J* = 6.0 Hz); ¹³C-NMR (150 MHz, CDCl₃) δ 189.1, 159.8, 158.4, 154.4, 137.7, 135.8, 128.7, 128.2, 127.2, 109.8, 97.4, 70.6, 66.8, 61.6, 61.3, 38.7.

(E)-7-(Benzyloxy)-3-(3-hydroxy-4-methoxybenzylidene)-5,6-dimethoxychroman-4-one (18a). To a solution of the 4-chromanone (**16**) (80 mg, 0.26 mmol) in benzene (5 mL) was added 3-hydroxy-4-methoxybenzaldehyde (58 mg, 0.38 mmol) and *p*-toluenesulfonic acid (7 mg, 0.03 mmol) at 0 °C. The reaction mixture was refluxed for 12 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate:*n*-hexane = 1:2) to afford the resulting 3-benzylidene-4-chromanone (**18a**) (60 mg, 53%). ¹H-NMR (600 MHz, CDCl₃) δ 7.73 (s, 1H), 7.42–7.38 (m, 4H), 7.35–7.33 (m, 1H), 6.90 (d, 1H, *J* = 8.4 Hz), 6.86–6.83 (m, 2H), 6.30 (s, 1H), 5.22 (d, 2H, *J* = 1.8 Hz), 5.13 (s, 2H), 3.99 (s, 3H), 3.94 (s, 3H), 3.85 (s, 3H); ¹³C-NMR (150 MHz, CDCl₃) δ 179.6, 159.2, 158.2, 154.9, 147.6, 145.5, 138.1, 136.3, 135.8, 130.1, 128.7, 128.2, 128.0, 127.2, 123.2, 115.8, 110.8, 110.6, 97.5, 70.6, 67.6, 61.7, 61.3, 56.0; HRMS (EI): mass calculated for C₂₆H₂₄O₇ [M⁺], 448.1522; found, 448.1521.

(E)-7-(Benzyloxy)-3-(4-hydroxy-3-methoxybenzylidene)-5,6-dimethoxychroman-4-one (18b). To a solution of the 4-chromanone (**16**) (80 mg, 0.26 mmol) in benzene (5 mL) was added 4-hydroxy-3-methoxybenzaldehyde (58 mg, 0.38 mmol) and *p*-toluenesulfonic acid (7 mg, 0.03 mmol) at 0 °C. The reaction mixture was refluxed for 12 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate:*n*-hexane = 1:2) to afford the resulting 3-benzylidene-4-chromanone (**18b**) (65 mg, 57%). ¹H-NMR (600 MHz, CDCl₃) δ 7.76 (s, 1H), 7.43–7.38 (m, 4H), 7.35–7.32 (m, 1H), 6.97 (d, 1H, *J* = 8.4 Hz), 6.82 (d, 1H, *J* = 1.8 Hz), 6.79 (dd, 1H, *J* = 7.8 and 1.8 Hz), 6.30 (s, 1H), 5.22 (d, 2H, *J* = 1.2 Hz), 5.13 (s, 2H), 3.99 (s, 3H), 3.91 (s, 3H), 3.85 (s, 3H); ¹³C-NMR (150 MHz, CDCl₃) δ 179.5, 159.1, 158.2, 154.9, 146.9, 146.5, 138.1, 136.5, 135.8, 129.8, 128.7, 128.2, 127.2, 127.1, 123.7, 114.6, 112.7, 110.8, 97.5, 70.6, 67.6, 61.7, 61.3, 56.0; HRMS (EI): mass calculated for C₂₆H₂₄O₇ [M⁺], 448.1522; found, 448.1521.

(E)-7-(Benzyloxy)-3-(3,4-bis(benzyloxy)benzylidene)-5,6-dimethoxychroman-4-one (18c). To a solution of the 4-chromanone (**16**) (80 mg, 0.25 mmol) in benzene (5 mL) was added 3,4-bis(benzyloxy)benzaldehyde (120 mg, 0.38 mmol) and *p*-toluenesulfonic acid (7 mg, 0.03 mmol) at 0 °C. The reaction mixture

was refluxed for 12 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate:*n*-hexane = 1:2) to afford the resulting 3-benzylidene-4-chromanone (**18c**) (55 mg, 36%). ¹H-NMR (600 MHz, CDCl₃) δ 7.68 (s, 1H), 7.46–7.31 (m, 15H), 6.96 (d, 2H, *J* = 9.0 Hz), 6.82 (dd, 2H, *J* = 4.8 and 3.0 Hz), 6.29 (s, 1H), 5.22 (s, 2H), 5.19 (s, 2H), 5.13 (s, 2H), 5.04 (d, 2H, *J* = 1.8 Hz), 3.98 (s, 3H), 3.85 (s, 3H); ¹³C-NMR (150 MHz, CDCl₃) δ 179.5, 159.1, 158.2, 154.9, 150.0, 148.4, 138.1, 136.8, 136.7, 136.1, 135.8, 130.1, 128.7, 128.6, 128.6, 128.4, 128.2, 128.0, 127.9, 127.5, 127.2, 127.2, 124.1, 116.9, 114.2, 110.8, 97.5, 71.4, 71.0, 70.6, 67.5, 61.7, 61.3; HRMS (EI): mass calculated for C₃₉H₃₄O₇ [M⁺], 614.2305; found, 614.2308.

(*E*)-7-(Benzyloxy)-3-(4-(benzyloxy)benzylidene)-5,6-dimethoxychroman-4-one (**18d**). To a solution of the 4-chromanone (**16**) (121 mg, 0.39 mmol) in benzene (5 mL) was added 4-(benzyloxy)benzaldehyde (122 mg, 0.58 mmol) and *p*-toluenesulfonic acid (7 mg, 0.03 mmol) at 0 °C. The reaction mixture was refluxed for 12 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate:*n*-hexane = 1:2) to afford the resulting 3-benzylidene-4-chromanone (**18d**) (104 mg, 54%). ¹H-NMR (600 MHz, CDCl₃) δ 7.78 (s, 1H), 7.44–7.38 (m, 8H), 7.35–7.33 (m, 2H), 7.24 (d, 2H, *J* = 9.0 Hz), 7.24 (dd, 2H, *J* = 6.6 and 1.8 Hz), 6.30 (s, 1H), 5.21 (d, 2H, *J* = 1.8 Hz), 5.13 (s, 2H), 5.11 (s, 2H), 4.00 (s, 3H), 3.85 (s, 3H); ¹³C-NMR (150 MHz, CDCl₃) δ 179.6, 159.6, 159.1, 158.2, 154.9, 138.1, 136.4, 136.1, 135.8, 131.7, 129.8, 128.7, 128.7, 128.2, 128.1, 127.5, 127.4, 127.2, 115.0, 110.8, 97.5, 70.6, 70.1, 67.6, 61.7, 61.3; HRMS (EI): mass calculated for C₃₂H₂₈O₆ [M⁺], 508.1886; found, 508.1885.

(*E*)-7-(Benzyloxy)-5,6-dimethoxy-3-(4-methoxybenzylidene)chroman-4-one (**18e**). To a solution of the 4-chromanone (**16**) (82 mg, 0.26 mmol) in benzene (5 mL) was added 4-methoxybenzaldehyde (50 μL, 0.39 mmol) and *p*-toluenesulfonic acid (7 mg, 0.03 mmol) at 0 °C. The reaction mixture was refluxed for 12 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate:*n*-hexane = 1:2) to afford the resulting 3-benzylidene-4-chromanone (**18e**) (78 mg, 75%). ¹H-NMR (600 MHz, CDCl₃) δ 7.78 (s, 1H), 7.44–7.38 (m, 8H), 7.35–7.33 (m, 2H), 7.24 (d, 2H, *J* = 9.0 Hz), 7.24 (dd, 2H, *J* = 6.6 and 1.8 Hz), 6.30 (s, 1H), 5.21 (d, 2H, *J* = 1.8 Hz), 5.13 (s, 2H), 5.11 (s, 2H), 4.00 (s, 3H), 3.85 (s, 3H); ¹³C-NMR (150 MHz, CDCl₃) δ 179.6, 159.6, 159.1, 158.2, 154.9, 138.1, 136.4, 136.1, 135.8, 131.7, 129.8, 128.7, 128.7, 128.2, 128.1, 127.5, 127.4, 127.2, 115.0, 110.8, 97.5, 70.6, 70.1, 67.6, 61.7, 61.3; HRMS (EI): mass calculated for C₂₆H₂₄O₆ [M⁺], 432.1573; found, 432.1573.

7-Hydroxy-3-(3-hydroxy-4-methoxybenzyl)-5,6-dimethoxychroman-4-one (**15a**). A solution of the 3-benzylidene-4-chromanone (**18a**) (35 mg, 0.07 mmol) and 10% Pd/C (10 mg) in MeOH was placed under an atmosphere of hydrogen. After stirring for 1 h, the reaction mixture was diluted with ethyl acetate, filtered through a Celite pad, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate:*n*-hexane = 1:1) to afford the 3-benzyl-4-chromanone (**15a**) (22 mg, 87%). ¹H-NMR (600 MHz, CD₃OD) δ 6.82 (d, 1H, *J* = 14.4 Hz), 6.67 (d, 1H, *J* = 1.8 Hz), 6.63 (dd, 1H, *J* = 8.4 and 2.4 Hz), 6.16 (s, 1H), 4.21 (dd, 1H, *J* = 11.4 and 4.2 Hz), 4.04 (dd, 1H, *J* = 11.4 and 7.2 Hz), 3.82 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 3.00 (dd, 1H, *J* = 13.2 and 4.2 Hz), 2.66–2.60 (m, 1H), 2.58 (dd, 1H, *J* = 13.8 and 10.8 Hz); ¹³C-NMR (150 MHz, CD₃OD) δ 192.4, 160.0, 158.5, 154.4, 146.3, 146.2, 136.4, 131.2, 119.9, 115.6, 111.5, 107.3, 99.1, 68.6, 60.4, 60.1, 55.0, 48.2, 32.0; HRMS (ESI): mass calcd for C₁₉H₂₀O₇ [M + H⁺], 361.1281; found 361.1270.

7-Hydroxy-3-(4-hydroxy-3-methoxybenzyl)-5,6-dimethoxychroman-4-one (**15b**). A solution of the 3-benzylidene-4-chromanone (**18b**) (21 mg, 0.05 mmol) and 10% Pd/C (5 mg) in MeOH was placed under an atmosphere of hydrogen. After stirring for 1 h, the reaction mixture was diluted with ethyl acetate, filtered through a Celite pad and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate:*n*-hexane = 1:1) to afford the 3-benzyl-4-chromanone (**15b**) (15 mg, 73%). ¹H-NMR (600 MHz, CDCl₃) δ 6.84 (d, 1H, *J* = 8.4 Hz),

6.73–6.69 (m, 2H), 6.31 (s, 1H), 4.26 (dd, 1H, $J = 11.4$ and 4.2 Hz), 4.10 (dd, 1H, $J = 11.4$ and 7.2 Hz), 3.91 (s, 3H), 3.91 (s, 3H), 3.87 (s, 3H), 3.16 (dd, 1H, $J = 13.8$ and 4.2 Hz), 2.73 (m, 1H), 2.65–2.61 (m, 1H); ^{13}C -NMR (150 MHz, CDCl_3) δ 191.6, 159.8, 155.5, 153.5, 146.5, 144.2, 135.2, 130.2, 121.9, 114.3, 111.4, 108.7, 98.8, 68.8, 61.5, 61.4, 55.9, 48.6, 32.6; HRMS (EI): mass calculated for $\text{C}_{19}\text{H}_{20}\text{O}_7$ [M^+], 360.1209; found, 360.1208.

3-(3,4-Dihydroxybenzyl)-7-hydroxy-5,6-dimethoxychroman-4-one (15c). A solution of the 3-benzylidene-4-chromanone (**18c**) (20 mg, 33 μmol) and 10% Pd/C (3.5 mg) in MeOH was placed under an atmosphere of hydrogen. After stirring for 1 h, the reaction mixture was diluted with ethyl acetate, filtered through a Celite pad and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate:*n*-hexane = 1:1) to afford the 3-benzyl-4-chromanone (**15c**) (11 mg, 99%). ^1H -NMR (600 MHz, CDCl_3) δ 6.79 (d, 1H, $J = 8.4$ Hz), 6.77 (d, 1H, $J = 2.4$ Hz), 6.63 (dd, 1H, $J = 8.4$ and 1.8 Hz), 6.30 (s, 1H), 4.26 (dd, 1H, $J = 11.4$ and 4.2 Hz), 4.09 (dd, 1H, $J = 8.4$ and 4.2 Hz), 3.90 (s, 3H), 3.89 (s, 3H), 3.08 (dd, 1H, $J = 13.8$ and 4.2 Hz), 2.70–2.67 (m, 1H), 2.62 (dd, 1H, $J = 13.8$ and 10.8 Hz); ^{13}C -NMR (150 MHz, CDCl_3) δ 192.2, 159.9, 155.9, 153.5, 143.8, 142.5, 135.2, 131.0, 121.6, 116.0, 115.3, 108.5, 98.9, 68.8, 61.5, 61.4, 48.5, 32.4; HRMS (EI): mass calculated for $\text{C}_{18}\text{H}_{18}\text{O}_7$ [M^+], 346.1053; found, 346.1056.

7-Hydroxy-3-(4-hydroxybenzyl)-5,6-dimethoxychroman-4-one (6). A solution of the 3-benzylidene-4-chromanone (**18d**) (23 mg, 0.05 mmol) and 10% Pd/C (5 mg) in MeOH was placed under an atmosphere of hydrogen. After stirring for 1 h, the reaction mixture was diluted with ethyl acetate, filtered through a Celite pad and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate:*n*-hexane = 1:1) to afford the 3-benzyl-4-chromanone (**6**) (14 mg, 94%). ^1H -NMR (600 MHz, CDCl_3) δ 7.09 (d, 2H, $J = 8.4$ Hz), 6.78 (d, 2H, $J = 8.4$ Hz), 6.30 (s, 1H), 4.62 (dd, 1H, $J = 11.4$ and 4.2 Hz), 4.08 (dd, 1H, $J = 11.4$ and 7.2 Hz), 3.91 (s, 3H), 3.90 (s, 3H), 3.15 (dd, 1H, $J = 13.8$ and 4.2 Hz), 2.73–2.69 (m, 1H), 2.66 (dd, 1H, $J = 13.8$ and 10.2 Hz); ^{13}C -NMR (150 MHz, CDCl_3) δ 191.7, 159.8, 155.6, 154.3, 153.5, 135.2, 130.3, 130.3, 115.4, 108.6, 98.8, 68.8, 61.5, 61.4, 48.5, 32.0; HRMS (EI): mass calculated for $\text{C}_{18}\text{H}_{18}\text{O}_6$ [M^+], 330.1103; found, 330.1102.

7-Hydroxy-5,6-dimethoxy-3-(4-methoxybenzyl)chroman-4-one (7). A solution of the 3-benzylidene-4-chromanone (**18e**) (23 mg, 0.05 mmol) and 10% Pd/C (5 mg) in MeOH was placed under an atmosphere of hydrogen. After stirring for 1 h, the reaction mixture was diluted with ethyl acetate, filtered through a Celite pad and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate:*n*-hexane = 1:2) to afford the 3-benzyl-4-chromanone (**7**) (13 mg, 80%). ^1H -NMR (600 MHz, CD_3COCD_3) δ 7.07–7.05 (m, 2H), 6.76–6.73 (m, 2H), 6.09 (dd, 1H, $J = 4.8$ and 3.0 Hz), 4.14 (d, 1H, $J = 4.2$ Hz), 3.94 (d, 1H, $J = 8.4$ Hz), 3.71 (s, 3H), 3.71–3.62 (m, 6H), 3.00–3.98 (m, 1H), 2.62–2.61 (m, 1H), 2.53–2.49 (m, 1H); ^{13}C -NMR (150 MHz, CDCl_3) δ 190.0, 159.6, 158.5, 157.1, 154.7, 136.3, 160.8, 130.8, 130.1, 113.9, 108.5, 99.1, 69.1, 60.8, 60.6, 54.6, 48.3, 31.5; HRMS (EI): mass calculated for $\text{C}_{19}\text{H}_{20}\text{O}_6$ [M^+], 344.1260; found, 344.1257.

7-Hydroxy-3-(3-hydroxy-4-methoxybenzyl)-5,6-dimethoxychroman-4-one (2). To a solution of the 7-hydroxy-5,6-dimethoxy-4-chromanone (**15b**) (10 mg, 0.03 mmol) in CH_2Cl_2 (5 mL) was added TMSI (5 μL , 0.09 mmol) at 0°C for 1 h. The mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (ethyl acetate:*n*-hexane = 1:2) to afford the 5,7-dihydroxy-6-methoxy-4-chromanone (**2**) (7.1 mg, 71%). ^1H -NMR (600 MHz, CD_3OD) δ 6.81 (d, 1H, $J = 1.8$ Hz), 6.73 (d, 1H, $J = 7.8$ Hz), 6.67 (dd, 1H, $J = 8.4$ and 1.8 Hz), 5.90 (s, 1H), 4.25 (dd, 1H, $J = 11.4$ and 4.2 Hz), 4.09 (dd, 1H, $J = 11.4$ and 7.2 Hz), 3.83 (s, 3H), 3.77 (s, 3H), 3.12 (dd, 1H, $J = 13.8$ and 4.8 Hz), 2.86–2.81 (m, 1H), 2.68 (d, 1H, $J = 10.2$ Hz); ^{13}C -NMR (150 MHz, CD_3OD) δ 199.3, 160.1, 159.3, 156.0, 148.2, 145.5, 130.0, 129.6, 121.9, 115.4, 112.8, 102.1, 95.0, 69.5, 60.1, 55.5, 47.3, 32.7; HRMS (EI): mass calculated for $\text{C}_{18}\text{H}_{18}\text{O}_7$ [M^+], 346.1053; found, 346.1054.

3-(3,4-Dihydroxybenzyl)-5,7-dihydroxy-6-methoxychroman-4-one (3). To a solution of the 7-hydroxy-5,6-dimethoxy-4-chromanone (**15c**) (20 mg, 0.03 mmol) in CH_2Cl_2 (5 mL) was added

TMSI (5 μ L, 0.09 mmol) at 0 $^{\circ}$ C for 1 h. The mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (ethyl acetate:*n*-hexane = 1:2) to afford the 5,7-dihydroxy-6-methoxy-4-chromanone (**3**) (12 mg, 99%). 1 H-NMR (600 MHz, CD₃OD) δ 6.71 (d, 1H, *J* = 8.4 Hz), 6.67 (d, 1H, *J* = 2.4 Hz), 6.55 (dd, 1H, *J* = 7.8 and 1.8 Hz), 5.91 (s, 1H), 4.24 (dd, 1H, *J* = 11.4 and 4.2 Hz), 4.08 (dd, 1H, *J* = 11.4 and 7.2 Hz), 3.77 (s, 3H), 3.05 (dd, 1H, *J* = 13.8 and 4.2 Hz), 2.80–2.75 (m, 1H), 2.60 (dd, 1H, *J* = 13.8 and 10.2 Hz); 13 C-NMR (150 MHz, CD₃OD) δ 200.0, 160.5, 159.9, 156.7, 146.2, 144.9, 130.6, 130.2, 121.2, 116.9, 116.2, 102.8, 95.5, 70.0, 60.7, 47.9, 33.0; HRMS (EI): mass calculated for C₁₇H₁₆O₇ [M⁺], 332.0896; found, 332.0898.

5,7-Dihydroxy-3-(4-hydroxybenzyl)-6-methoxychroman-4-one (**4**). To a solution of the 7-hydroxy-5,6-dimethoxy-4-chromanone (**6**) (10 mg, 0.03 mmol) in CH₂Cl₂ (5 mL) was added TMSI (5 μ L, 0.09 mmol) at 0 $^{\circ}$ C for 1 h. The mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (ethyl acetate:*n*-hexane = 1:2) to afford the resulting 5,7-dihydroxy-6-methoxy-4-chromanone (**4**) (9.8 mg, 86%). 1 H-NMR (600 MHz, CD₃OD) δ 7.06 (d, 2H, *J* = 8.4 Hz), 6.73 (d, 2H, *J* = 8.4 Hz), 5.90 (s, 1H), 4.23 (dd, 1H, *J* = 11.4 and 4.2 Hz), 4.07 (dd, 1H, *J* = 10.8 and 7.2 Hz), 3.77 (s, 3H), 3.10 (dd, 1H, *J* = 13.8 and 4.8 Hz), 2.82–2.77 (m, 1H), 2.67 (dd, 1H, *J* = 13.8 and 10.2 Hz); 13 C-NMR (150 MHz, CD₃OD) δ 199.8, 160.4, 159.7, 156.8, 156.5, 130.7, 130.0, 129.7, 116.0, 102.5, 95.4, 69.8, 60.5, 47.8, 32.6; HRMS (EI): mass calculated for C₁₇H₁₆O₆ [M⁺], 316.0947; found, 316.0945.

5,7-Dihydroxy-6-methoxy-3-(4-methoxybenzyl)chroman-4-one (**5**). To a solution of the 7-hydroxy-5,6-dimethoxy-4-chromanone (**7**) (19 mg, 0.06 mmol) in CH₂Cl₂ (5 mL) was added TMSI (10 μ L, 0.18 mmol) at 0 $^{\circ}$ C for 1 h. The mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (ethyl acetate:*n*-hexane = 1:2) to afford the resulting 5,7-dihydroxy-6-methoxy-4-chromanone (**5**) (15 mg, 80%). 1 H-NMR (600 MHz, CD₃OD) δ 7.15 (d, 2H, *J* = 8.4 Hz), 6.86 (d, 2H, *J* = 8.4 Hz), 5.90 (s, 1H), 4.23 (dd, 1H, *J* = 11.4 and 4.2 Hz), 4.06 (dd, 1H, *J* = 11.4 and 7.8 Hz), 3.77 (s, 3H), 3.76 (s, 3H), 3.13 (dd, 1H, *J* = 13.8 and 4.8 Hz), 2.84–2.79 (m, 1H), 2.70 (dd, 1H, *J* = 13.8 and 10.2 Hz); 13 C-NMR (150 MHz, CD₃OD) δ 200.1, 160.7, 160.1, 160.0, 156.9, 131.4, 131.2, 130.4, 115.1, 103.0, 95.8, 70.3, 61.0, 55.7, 48.1, 32.9; HRMS (EI): mass calculated for C₁₈H₁₈O₆ [M⁺], 330.1103; found, 330.1102.

(E)-7-Hydroxy-5,6-dimethoxy-3-(4-methoxybenzylidene)chroman-4-one (**19**). A solution of the 3-(4-methoxybenzylidene)-4-chromanone (**18e**) (37 mg, 0.09 mmol) and 3% Pd/C (4.8 mg) in MeOH was placed under an atmosphere of hydrogen. After stirring for 5 min, the reaction mixture was diluted with ethyl acetate, filtered through a Celite pad and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate:*n*-hexane = 1:3) to afford the debenzylated 3-(4-methoxybenzylidene)-4-chromanone (**19**) (11 mg, 35%). 1 H-NMR (600 MHz, CDCl₃) δ 7.78 (s, 1H), 7.26 (d, 2H, *J* = 7.8 Hz), 6.96 (d, 2H, *J* = 9.0 Hz), 6.31 (s, 1H), 5.22 (d, 2H, *J* = 1.8 Hz), 3.97 (s, 3H), 3.94 (s, 3H), 3.85 (s, 3H); 13 C-NMR (100 MHz, CDCl₃) δ 179.7, 160.4, 159.4, 155.3, 153.8, 136.2, 135.4, 131.7, 129.6, 127.1, 114.1, 110.4, 98.9, 67.4, 61.5, 61.4, 55.3; HRMS (EI): mass calculated for C₁₉H₁₈O₆ [M⁺], 342.1103; found, 342.1106.

(E)-5,7-Dihydroxy-6-methoxy-3-(4-methoxybenzylidene)chroman-4-one (**8**). To a solution of the 3-(4-methoxybenzylidene)-4-chromanone (**19**) (15 mg, 0.04 mmol) in CH₂Cl₂ (5 mL) was added TMSI (13 μ L, 0.09 mmol) at 0 $^{\circ}$ C for 1 h. The mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (ethyl acetate:*n*-hexane = 1:3) to afford the resulting 5,7-dihydroxy-6-methoxy-4-chromanone (**8**) (9.1 mg, 63%). 1 H-NMR (600 MHz, CDCl₃) δ 7.80 (s, 1H), 7.27 (d, 2H, *J* = 7.2 Hz), 6.97 (d, 2H, *J* = 8.4 Hz), 6.03 (s, 1H), 5.28 (d, 2H, *J* = 1.8 Hz), 3.95 (s, 3H), 3.86 (s, 3H); 13 C-NMR (100 MHz, CDCl₃) δ 185.9, 160.8, 157.8, 157.2, 155.2, 137.2, 132.0, 128.4, 127.3, 126.7, 114.2, 103.3, 94.0, 67.4, 60.9, 55.4; HRMS (EI): mass calculated for C₁₈H₁₆O₆ [M⁺], 328.0947; found, 328.0945.

4. Conclusions

In summary, we have successfully demonstrated the first total synthesis of naturally occurring homoisoflavonoids containing either a 7-hydroxy-5,6-dimethoxy or 5,7-dihydroxy-6-methoxy group on the A ring in four or five steps from the commercially available **11**. The key features of this synthetic route involve the following: (1) LiAlH₄-mediated selective 1,4-reduction of 4-chromenone; (2) the aldol condensation of arylaldehydes, followed by catalytic hydrogenation; (3) TMSI-mediated C5-demethylation; (4) the selective debenzoylation of 3-benzylidene-4-chromanone. These studies provide a timely contribution to the development of a practical synthetic approach to a variety of homoisoflavonoid analogues. Extension of this approach in the synthesis of various natural products and analogues and establishment of structure-activity relationship (SAR) profiles for 5,6,7-trisubstituted homoisoflavonoids compared to antiangiogenic cremastranone are currently underway.

Supplementary Materials: Supplementary materials can be accessed at: <http://www.mdpi.com/1420-3049/21/8/1058/s1>.

Acknowledgments: This work was supported by grants from the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2013R1A1A2007151) and the Korea Health Technology R & D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare (HI14C1135) to S.-Y.S.; grants from the Bright Focus Foundation, and NIH/NEI R01EY025641 to T.W.C., and an unrestricted grant from Research to Prevent Blindness, Inc.

Author Contributions: H.L. and Y.Y. performed the experiments and analyzed all data. I.R. and T.W.C. conceived and suggested the research work. S.-Y.S. conceived and directed the investigations and composed the manuscript with revisions provided by the other authors. All authors read and approved the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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Sample Availability: Samples of the compounds 1–8 are available from the authors.



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