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Efficient synthesis of analogs of safflower yellow B, carthamin, and its precursor: two yellow and one red dimeric pigments in safflower petals

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Abstract—The synthesis of analogs (**8**, **12**, **14**) of two yellow pigments, safflower yellow B and the precursor of carthamin, and carthamin itself, a red pigment, which are produced in safflower (*Carthamus tinctrious* L.) petals and, which have a common dimeric quinochalcone structure, is reported. The key compound for the synthesis of these analogs, (*p*-hydroxycinnamoyl)filicinic acid (**7**) was synthesized in six steps from phloroglucinol in a total yield of 39%, which was reacted with 2,3,4,5,6-penta-*O*-acetyl-aldehydo-D-glucose, glyoxylic acid, and ethyl orthoformate in the presence of base to afford the corresponding analog, **8**, **12**, **14**, in good yields, respectively. Precursor analog **12** was then converted to carthamin analog **14** by oxidative decarboxylation by treatment with potassium permanganate as well as the natural specimen.

1. Introduction

Carthamin (**5**),[1] a brilliant-red component of the flower petals of the safflower has long been used as a dye, rouge, and Chinese medicine. Currently, **5** and the water-soluble yellow components of safflower petals are used as a natural food colorant. The major yellow components of safflower petals, safflomin-A (**2**),[1b,2] safflower yellow B (**1**),[3] safflomin-C (**3**),[4] and carthamin precursor (**4**)[5] were isolated and their structures were elucidated. In addition, recently the *N*-containing yellow pigments, tinctromin[6] and cartormin[7] have also been isolated from safflower petals and their structures were elucidated. The above pigments share a unique *C*-glycosylquinochalcone, which has not been found in any other naturally occurring products to date.

The recently proposed[8] biosynthetic pathway of the main pigments, starting from **1**, is shown in Figure 1; the hydrolysis of **1** forms **2** and an unstable *C*-glycosylquinochalcone (**6**),[8] which rapidly reacts with glyoxylic acid or *p*-hydroxycinnamic acid to form the yellow pigments, **4** or **3**. Because **4** is unstable, it readily undergoes oxidative decarboxylation to the red pigment **5**. The biosynthesis of **1** has not been reported, but it is assumed that **1** is formed by the condensation of 2 equiv of reactive **6** and 1 equiv of D-glucose. The unstable **6** can be formed by the oxidation of *C*-glucosylchalcone or the glycosylation of pentahydroxychalcone.[8b]

In the total synthesis of these pigments, asymmetric synthesis of **5** (as the acetate) has been achieved,[9] and the stereochemistry of its chiral carbon was determined to be *S*.[10] The total synthesis of the other yellow pigments have not yet been carried out, but the synthesis of analogs (**9**, **10**, **11**, **12**, **13**, and **14**) in which the glucosyl group, or the glucosyl and hydroxyl groups on the chiral carbon were replaced by one or two methyl groups has been achieved for **2**,[11a] **3**,[11b] **4**,[11e], and **5**.[11c,d] Since the *C*-glucopyranosylquinochalcone structure is unique and is present as a complex mixture of keto–enol tautomers, we have synthesized analogs of these pigments as model compounds, and explored the characteristics and behavior of these unique quinochalcone pigments, and further proved the proposed structure. However, the yield was unsatisfactory, and the synthesis of an analog (**8**) of safflower yellow B (**1**), which has the characteristic dimeric structure cross-linked with a 1-deoxyglucitol, has not yet been reported.

Keywords: Safflower petals; Yellow and red pigments; Safflower yellow B; Carthamin; Carthamin precursor; Analog; (*p*-Hydroxycinnamoyl)filicinic acid.
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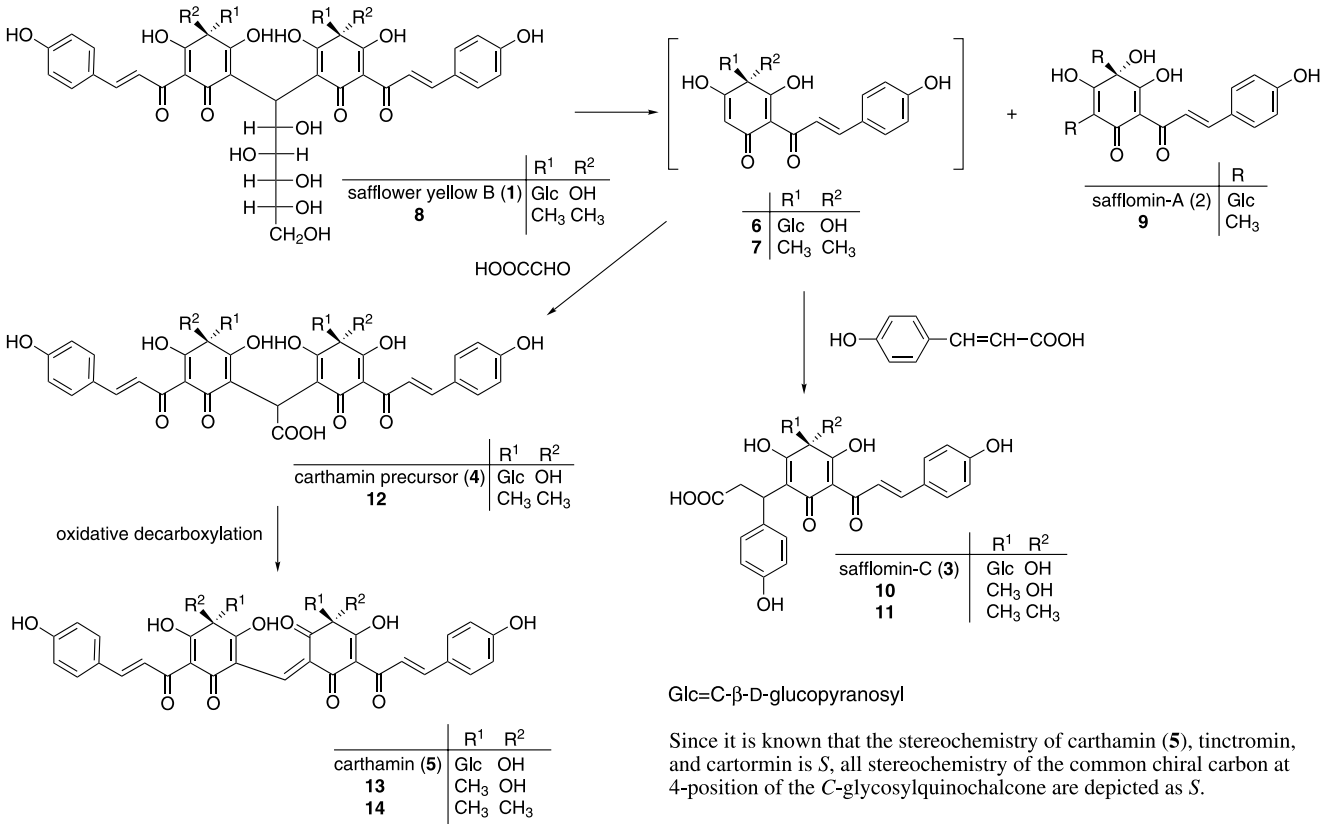


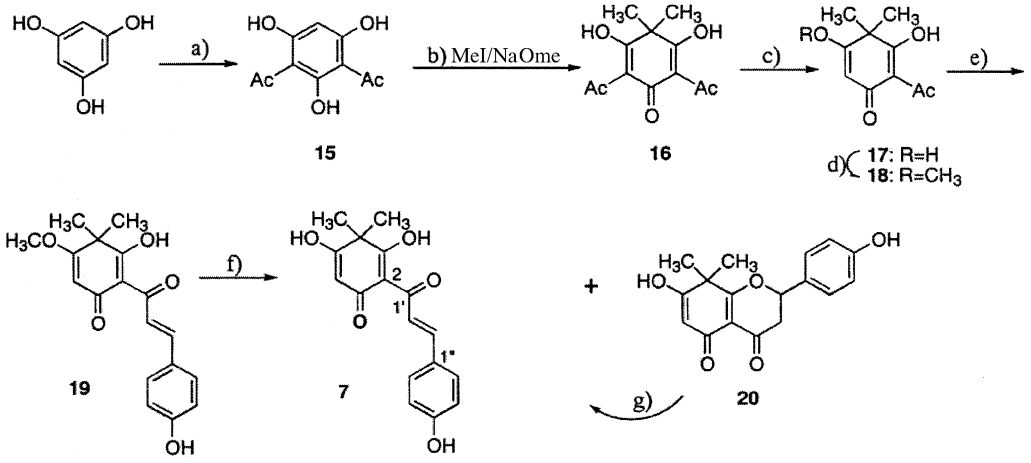
Since it is known that the stereochemistry of carthamin (**5**), tinctromin, and cartormin is *S*, all stereochemistry of the common chiral carbon at 4-position of the *C*-glycosylquinochalcone are depicted as *S*.

Figure 1. Proposed biosynthetic pathway for the yellow and red pigments from safflower yellow B in safflower petals and their analogs.

Herein, we wish to report on the efficient synthesis of analogs (**8**, **12**, and **14**) of the above three dimeric pigments (**1**, **4**, and **5**), in which both the *C*-glucosyl and hydroxyl group on the chiral carbon are replaced by methyl groups. The key compound in the synthesis of the analog of these dimeric pigments, (*p*-hydroxycinnamoyl)filicinic acid (**7**), which is also a stable analog of the reactive and unstable *C*-glucopyranosylquinochalcone (**6**), was able to be synthesized in six steps from phloroglucinol in a total yield of 39%, via the improvement of the yield.

2. Results and discussion

The synthesis of **7**, a key-compound in the synthesis of the three dimeric analogs **8**, **12**, and **14**, was carried out by modifying the previous method[11c,e,12] as follows (see Scheme 1); phloroglucinol was diacetylated by heating at 100 °C in the presence of boron trifluoride acetic acid complex ($BF_3 \cdot 2AcOH$) to give diacetylphloroglucinol (**15**) in 84% yield. Diacetylphloroglucinol (**15**) was then methylated by reaction with iodomethane in the presence

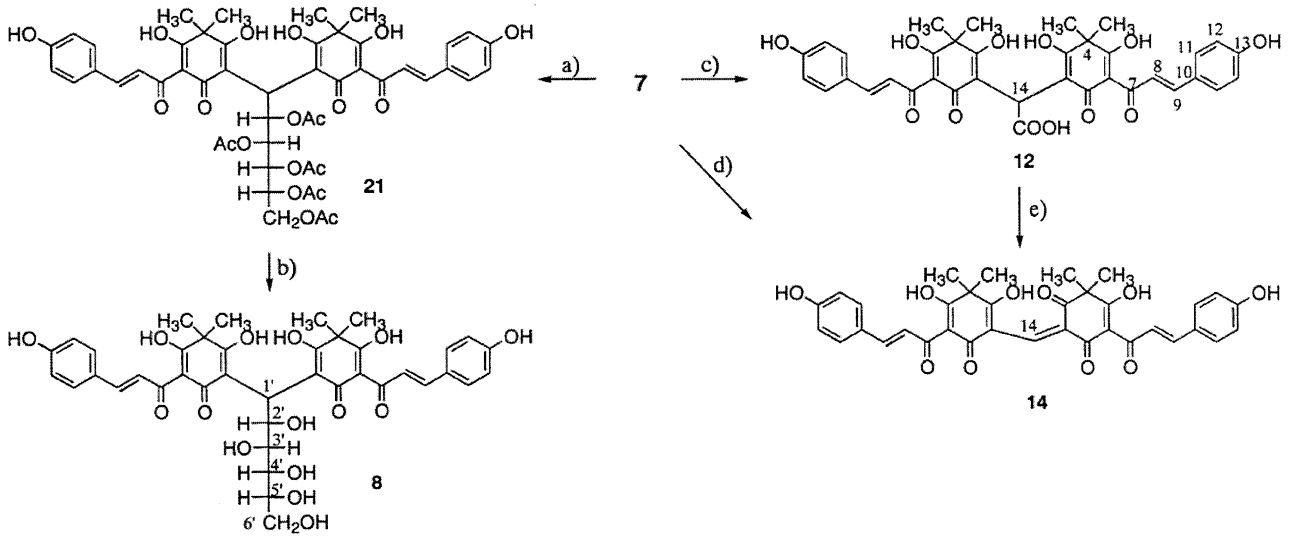


Scheme 1. Efficient synthesis of the key-compound (**7**) in the synthesis of analogs of pigments in safflower petals. Reagents and conditions: (a) $BF_3 \cdot 2AcOH$, 100 °C, 2 h, Y: 84%; (b) MeI/NaOme, Y: 78%; (c) 80% H_2SO_4 aqueous solution, 80 °C, 50 min, Y: 89%; (d) CH_2N_2, Y: 99%; (e) *p*-hydroxybenzaldehyde (4 equiv)/piperidine, 80 °C, 1 h, Y: 79%; (f) 28% HBr–AcOH, 70 °C, 0.5 h, Y: 68% for **7**, 15% for **20**; (g) NaOMe, Y: 60%.

of sodium methoxide (NaOMe) to give 2,4-diacetyl-6,6-dimethylcyclohexa-1,3,5-trione (**16**) in 78% yield, which was then mono-deacetylated by heating at 80 °C for 50 min in an 80% H_2SO_4 aqueous solution to give acetylfilicinic acid (**17**) in 89% yield. In the previous paper,[11c] after benzoylphloroglucinol was acetylated, **7** was synthesized by aldol reaction followed by debenzoylation. However, the yield of final debenzoylation was low. Furthermore, **7** has been synthesized by mono-aldol condensation of diacetylfilicininc acid followed by selective deacetylation, however, the yield by this method was also low due to the poor selectivity.[11e] To prevent side-reactions at the 6-position of **17** in the next aldol reaction, the enol-hydroxyl group of **17** was selectively methylated by treatment with diazomethane to give 2-acetyl-3-hydroxy-5-methoxy-4,4-dimethylcyclohexa-2,5-dienone (**18**) as colorless prisms in quantitative yield. Aldol condensation of cyclohexadienone **18** with *p*-hydroxybenzaldehyde (4 equiv) in piperidine at 80 °C for 1 h afforded the desired 2-cinnamoyl-5-*O*-methylfilicinic acid (**19**) in 79% yield. Since the yield of de-*O*-methylation reaction of **19** by refluxing in concd HCl–methanol was poor due to its low solubility,[12] de-*O*-methylation by heating at 70 °C for 0.5 h in a 28% HBr acetic acid solution was carried out to give the desired cinnamoylfilicinic acid **7** and its ring-closed flavanone **20** in 68 and 15% yield, respectively. Flavanone **20** was then partially ring-opened by treatment with NaOMe to give **7** in 60% yield.

With the key-compound **7** in hand, we initially examined the first synthesis of **9** the condensation of 2 equiv of **7** with an aldehydo-glucose in the presence of NaOMe. Three aldehydo-glucose derivatives were prepared by the acetonide-, benzyl-, or acetyl-protection of the 2,3,4,5,6-hydroxyl groups. The results for each of the condensation reactions of **7** and these aldehydo-glucose derivatives was satisfactory, but the subsequent deprotection of the glucitol moiety of the resulting dimer was difficult. Deprotection of the acetonide by treatment with a weak acid or even hydrogenolysis of the benzyl protecting group gave a mixture of xanthene-type products, which were produced by dehydration and ring-closure between two enol-hydroxyl groups. However, removal of the acetate groups under alkaline conditions gave the desired compound **8**, as follows; 2 equiv of **7** were condensed with 1 equiv of 2,3,4,5,6-penta-*O*-acetyl-aldehydo-D-glucose[17,18] prepared from D-glucose via three steps in a 78% yield in the presence of catalytic amount of NaOMe in dry methanol at room temperature for 5 h, followed by de-*O*-acetylation with a 28% NaOMe methanol solution. Although the de-*O*-acetylation partially proceeded under these condensation reaction conditions, the desired dimer **21** and its partial de-*O*-acetates were obtained in a total yield of 75–85%. Purification of their de-*O*-acetylation products by silica gel and Sephadex column chromatography gave an analog **8** of safflower yellow B (**1**) as a yellow powder in a yield of 71% from **7** (Scheme 2).

The synthesis of an analog **12** of carthamin precursor (**4**) was achieved by a coupling reaction of 2 equiv of **7** with 1 equiv of glyoxylic acid employing the same alkaline conditions as for the synthesis of **21**. The reaction proceeded smoothly to afford **12** as the sole product, in an excellent 99% yield.[11d] In the ^{1}H NMR spectrum of **12** in pyridine-d_5, the methine proton of the central acetic acid moiety appeared at a low field of δ 7.15 ppm, which was confirmed by C–H COSY between the methine carbon (δ_C 34.8 ppm). In the synthesis of carthamin analog **14**, the coupling of **7** with triethyl orthoformate did not proceed under alkaline conditions using NaOMe as well as the synthesis of **21**, and **12**. However, in the presence of 12.5 equiv of sodium hydride (NaH),[11c] the reaction proceeded smoothly, affording **14** as the sole product. After recrystallization the overall yield was 90%. The precursor analog **12** was then subjected to oxidative decarboxylation by treatment with an aqueous solution of permanganate at room temperature to give **14** in 52% yield as well as the natural specimen.[5b] Both the ^{1}H and ^{13}C NMR spectra of **8**, **12**, and **14** in DMSO-d_6 gave unsymmetrical and complicated spectra due to the complex mixture of keto–enol tautomers. However, the use of pyridine-d_5 as a solvent gave symmetrical and simple



Scheme 2. Synthesis of analogs (**8**, **12**, and **14**) of the three dimeric yellow and red pigments in safflower petals via quinocalcone **7**. Reagents and conditions: (a) 2,3,4,5,6-penta-*O*-acetyl-aldehydo-D-glucose/NaOMe; (b) NaOMe or 10% NaOH aqueous solution-MeOH, Y: 71% (from **7**); (c) HO_2CCHO/NaOMe, Y: 99%; (d) $HC(OEt)_3$/NaH, Y: 90%; (e) 0.23% $KMnO_4$ aqueous solution in acetone, Y: 52%.

spectra. ^{1}H and ^{13}C NMR spectra of the 1-deoxyglucitol moiety of **8** were very analogous to those of **1**, except for the coupling constants between H3 and H4 (**8**: $J_{3,4}=\sim 0$ Hz.; **1**[8b]: $J_{3,4}=7.0$ Hz). The UV–vis spectra of **8**, **12**, and **14** were also very analogous to the natural specimen and they were liable to including a solvent such as water, alcohol, or ethyl acetate. Yellow-colored **12** was converted to red-colored **14** by treatment of peroxidase–H_2O_2 solution as well as the natural specimen. Carthamin analog **14** also dyed silk and cotton pink-red in a similar way to the natural specimen.

3. Conclusion

We established an efficient method for the synthesis of an analog of the main dimeric pigments in safflower petals, by using the key compound, (*p*-hydroxycinnamoyl)filicinic acid (**7**). Since spectral data for each synthesized analog was quite analogous to its natural specimen, it was supported that the proposed structure of three dimeric pigments was appropriate. We are currently attempting the total synthesis of the main yellow pigments in safflower petals on the basis of this result.

4. Experimental

4.1. General

The solvents used in this reaction were prepared by distillation. The synthesized compounds were separated and purified by flash column chromatography using silica gel (Fuji-Silysia Co., Ltd, BW-300) and by column chromatography using Sephadex LH-20 gel (Amersham Pharmacia Biotech AB). Melting points were determined on a Shibayama micro-melting point apparatus and are uncorrected. UV–vis spectra were recorded on a Hitachi U-2010 spectrophotometer. Optical rotations were recorded on a JASCO DIP-370 polarimeter. Mass spectral data were obtained by electron ionization (EI) or fast-atom bombardment (FAB) using 3-nitrobenzyl alcohol (NBA), glycerol, or thioglycerol as the matrix on a JEOL JMS-AX505HA instrument. IR spectra were recorded on a Horiba FT-720 IR spectrometer. NMR spectra were recorded on a Varian Inova 500 spectrometer using Me_4Si as an internal standard.

4.2. Synthesis of the key-compound, (*p*-hydroxycinnamoyl) filicinic acid; 2-[3′-(*p*-hydroxyphenyl)-2′-propenoyl]-3,5-dihydroxy-6,6-dimethyl-2,4-cyclohexadien-1-one (7)

4.2.1. Diacetylphloroglucinol (15). A solution of phlroglucinol (20.0 g, 158 mmol) in $BF_3\cdot 2AcOH$ (95 mL) was stirred on an oil bath at 100 °C for 3 h. The reaction mixture was cooled to room temperature and then poured into 1 L of an aqueous KOAc (50.1 g/L) solution and the mixture was stirred for 3 h. The precipitated orange prisms were collected by filtration. The crude product was recrystallized from hot water–methanol to give **15** (23.6 g, 71%) as pale-yellow prisms. Colorless prisms. Mp 173–174 °C (lit.[13] 168 °C). ^{1}H NMR (DMSO-d_6) δ 2.60 (6H, s, $COCH_3\times 2$), 5.87 (1H, s, ArH), 13.23 (2H, s, OH), 16.30 (1H,s,OH).

4.2.2. 2,6-Diacety1-4,4-dimethylcyclohexan-1,3,5-trione (16).[12] Colorless prisms. Mp 65–66 °C (lit.[14] mp 65–66 °C). ^{1}H NMR ($CDCl_3$) δ 1.45 (6H, s, $CH_3\times 2$), 2.62 and 2.75 (each 3H, s, $COCH_3\times 2$), 18.87 and 19.20 (each 1H, s, OH).

4.2.3. Acetylfilicinic acid; 2-acetyl-4,4-dimethylcyclohexan-1,3,5-trione (17).[12] Colorless prisms. Mp 172–174 °C (lit.[15] 174–176 °C). ^{1}H NMR (DMSO-d_6) δ 1.28 (6H, s, $CH_3\times 2$), 2.47 (3H, s, $COCH_3$), 5.43 (1H, s, olefinic H), 18.41 (1H, s, OM. ^{13}C NMR (DMSO-d_6) δ 24.6 (CH_3), 28.3 ($CO\mathit{CH}_3$), 48.7 (C4), 94.9 (C6), 105.2 (C2), 182.5 (C=O), 188.7, 196.7, and 200.5 (C1, 3, 5).

4.2.4. 2-Acetyl-2-hydroxy-5-methoxy-4,4-dimethyl-2,5-cyclohexadien-1-one (18).[12] Colorless prisms. Mp 108–109 °C (lit.[12,16] 107–109 °C). IR (KBr) ν 2989, 2945, 1651, 1614, 1508 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.36 (6H, s, $CH_3\times 2$), 2.60 (3H, s, $COCH_3$), 3.82 (3H, s, OCH3), 5.42 (1H, s, olefinic H), 18.44 (1H, s, OH). EI-MS (*m*/*z*) 210 (M^+).

4.2.5. 2-[3-(*p*-Hydroxyphenyl)-2-propenoyl]-3-hydroxy-5-methoxy-6,6-dimethyl-2,4-cyclohexadien-1-one (19).[12] Yellow prisms. Mp 137–138 °C (lit.[16] 138–140 °C). IR (KBr) ν 3159, 3020, 2993, 2947, 1599, 1440 cm^{-1}. ^{1}H NMR ($CDCl_3$ including a small amount of DMSO-d_6) δ 1.39 (6H, s, $CH_3\times 2$), 3.83 (3H, s, OMe), 5.49 (1H, s, olefinic H), 6.87 and 7.56 (each 2H, d, $J=8.3$ Hz, *p*-substituted ArH), 7.90 and 8.12 (each 1H, d, $J=15.9$ Hz, *trans*-vinyl H), 9.37 (1H, s, ArOH), 19.00 (1H, s, OH). ^{13}C NMR (DMSO-d_6) δ 24.4 (CH_3), 57.1 (OCH_3), 48.6 (C6), 95.4 (C4), 104.6 (C2), 116.1 (C3″), 119.0 (C2′), 130.9 (C2″), 144.9 (C3′), 160.6 (C4″), 179.9 (C1′), 186.8 (C5), 190.5 (C3), 196.4 (C1). EI-MS (*m*/*z*) 314 (M^+).

4.3. De-*O*-methylation of 19

Methyl enol–ether **15** (1.187 g, 3.780 mmol) was added to 24 mL of a 33% HBr–acetic acid solution, and the mixture was stirred at 80 °C for 0.5 h. The reaction mixture was poured into ice-cold water (100 mL). The precipitated yellow powder was filtered and washed with water. The filtrate was extracted twice with EtOAc. The EtOAc extract was washed with water and brine, and then dried over anhydrous Na_2SO_4. After removing the organic solvents, the residual yellow solid and the above yellow powder were crystallized from EtOAc to give **7** (604 mg, 53%) as a yellow powder. The filtrate was separated by flash column chromatography on silica gel (6:1:0.1 toluene–EtOAc–AcOH) to give **7** (170 mg, 15%) as a yellow powder and **20** (178 mg, 15%) as a pale-yellow, solid.

4.3.1. *p*-Hydroxycinnamoylfilicinic acid; 2-[3′-(*p*-hydroxyphenyl)-2′-propenoyl]-3,5-dihydroxy-6,6-dimethyl-2,4-cyclohexndien-1-one (7). Yellow powder. Mp 205–206 °C (lit.[11c] 204–206 °C).UV–vis (EtOH) λ_{max} (log ε) 393 (4.39) nm (lit.[11c] 405 (4.5)). IR (KBT) ν 3159, 1593, 1416, 1234, 1165 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 1.32 (6H, s, $CH_3\times 2$), 5.51 (1H, s, olefinic H), 6.87 (2H, d, $J=8.5$ Hz, *p*-substituted ArH$\times 2$), 7.56 (2H, d, $J=8.5$ Hz, *p*-substituted ArH$\times 2$), 7.79 (1H, d, $J=15.9$ Hz, *trans*-vinyl H), 8.10 (1H, d, $J=15.9$ Hz, *trans*-vinyl H), 10.17 (1H, s, OH), 12.45 (1H, br. s, enol OH), 19.12 (1H, s, OH). ^{13}C NMR (DMSO-d_6) δ 24.4 ($CH_3\times 2$), 48.6 (C6), 96.5 (C4), 104.3 (C2), 116.1 (C3″ 5″), 119.5 (C-2′), 125.9 (C1″), 130.7 (C2″, 6″), 144.0 (C3′), 160.4 (C4″), 181.4 (C1′), 186.5 (C5), 190.4

(C3), 197.0 (C1). ^{1}H NMR (C_5D_5N) δ 1.63 (6H, s, $CH_3\times2$), 5.87 (1H, s, olefinic H), 7.16 (2H, d, $J=8.6$ Hz, *p*-substituted ArH×2), 7.73 (2H, d, $J=8.6$ Hz, *p*-substituted ArH×2), 8.29 (2H, d, $J=15.6$ Hz, *trans*-vinyl H), 8.86 (2H, d, $J=15.6$ Hz, *trans*-vinyl H). ^{13}C NMR (D_5D_5N) δ 25.2 ($CH_3\times2$), 50.1 (br. s, quaternary C), 97.2, 105.6, 117.0, 121.0, 127.2, 131.4, 144.6, 161.9, 183.7, 187.8, 192.7, 198.2. FAB-MS (NBA, *m/z*) 301 $(M+H)^+$. Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 68.10; H, 5.39.

4.3.2. 7-Hydroxy-2-(4-hydroxyphenyl)-8,8-dimethyl-3,4-dihydro-2*H*-1-benzopyran-4,5(8*H*)-dione (20). Yellow powder. Mp 188.5 °C (dec). UV–vis (EtOH) λ_{max} (log ε) 229 (4.29), 283 (4.08), 357 (3.73) nm. IR (KBr) ν 3300, 2981, 1670, 1627, 1616, 1533, 1520, 1456, 1414, 12591, 1223, 1144 cm^{-1}. ^{1}H NMR ($CDC1_3$+DMSO-d_6) δ 1.40 and 1.43 (each 3H, s, $CH_3\times2$), 2.85 (1H, dd, $J=3.0$, 18.5 Hz, $>CH_2$), 3.11 (1H, dd, $J=18.5$, 11.5 Hz, $>CH_2$), 5.24 (1H, dd, $J=3.0$, 11.5 Hz, >CH–), 5.47 (1H, s, olefinic H), 6.91 (2H, d, $J=8.5$ Hz, *p*-substituted ArH×2), 7.24 (2H, d, $J=8.5$ Hz, *p*-substituted ArH×2), 9.03 (1H, s, OH), 16.0 (1H, s, OH). FAB-MS (NBA, *m/z*) 301 $(M+H)^+$. Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 68.15; H, 5.50.

4.4. The conversion of 20 to 7

To a stirred solution of **20** (178 mg, 0.593 mmol) in dry MeOH (1.5 mL), 28% NaOMe (60 mg) was added dropwise at room temperature and the mixture was stirred for 1 h. The reaction mixture was neutralized by the addition of Dowex 50W (H^+) resins, and then filtered and washed with MeOH. The filtrate was evaporated in vacuo to give a brown solid, which was separated by column chromatography on silica gel (6:1:0.1 toluene–EtOAc–AcOH) to give **7** (107 mg, 60%) as a yellow powder and **20** (26.5 mg, 15%) as a pale-yellow solid.

4.5. Synthesis of the analogs (14, and 12) of carthamin and its precursor

4.5.1. 2,2-Bis[3-(*p*-hydroxycinnamoyl)filicinic acid-5-yl] acetic acid (12). To a stirred suspension of **7** (52.4 mg, 0.175 mmol) in dry methanol (1 mL), a 25% solution of NaOMe in methanol was added dropwise until **7** dissolved completely. To the stirred mixture, glyoxylic acid monohydrate (8.5 mg, 0.092 mmol) was added and the reaction mixture was further stirred at room temperature for 4 h until **7** disappeared by TLC monitoring (6:1:0.2 or 5:2:0.5 toluene–EtOAc–AcOH). The reaction mixture was poured into 15 mL of ice-cold 2 M HCI and extracted three times with EtOAc, The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was separated by flash column chromatography on silica gel (6:1:0.1 toluene–EtOAc–AcOH) to give **12** (56.6 mg, 99%) as a yellow powder.

Mp 195–198 °C (lit.[11e] 195 °C (dec)). Silica gel TLC: R_f 0.43 (5:2:0.5 toluene–EtOAc–AcOH). HPLC: t_R 7.28 min (80:20 MeOH–25% AcOH aqueous solution). UV–vis (EtOH) λ_{max} (log ε) 221 (4.55), 397 (4.74) nm; carthamin precursor (**4**): lit.[5b] MeOH λ_{max} (log ε) 238 (4.37), 406 (4.67) nm; lit.[5a] EtOH λ_{max} (log ε) 343 (4.25), 423 (4.56) nm. IR (KBr) ν 3406, 2983, 1618, 1601, 1516, 1414 cm^{-1}. ^{1}H NMR (C_5D_5N) δ 1.74 and 1.89 (each 6H, s, $CH_3\times6$), 7.09 (4H, d, $J=8.5$ Hz, *p*-substituted ArH×4), 7.15 (1H, s, >CH–), 7.63 (4H, d, $J=8.5$ Hz, *p*-substituted ArH×4), 8.17 (2H, d, $J=15.8$ Hz, *trans*-vinyl H), 8.90 (2H, d, $J=15.8$ Hz, *trans*-vinyl H). ^{13}C NMR (C_5D_5N) δ 24.6, 26.9 (CH_3), 34.8 (>CH–), 52.1 (quaternary C), 105.5, 107.7, 116.8, 123.4, 127.8, 130.8, 136.0, 161.0, 175.9, 186.0, 188.4, 189.1, 199.7. FAB-MS (NBA, *m/z*) 657 $(M+H)^+$. Anal. Calcd for $C_{36}H_{32}O_{12}$ $0.1H_2O$: C, 65.67; H, 4.93. Found: C, 65.44; H, 5.31.

4.5.2. Dehydro-3,3′-bis(*p*-hydroxycinnamoyl)-5,5′-methylenedifilicinic acid (14). To a stirred suspension of **7** (60 mg, 0.2 mmol) in ethyl orthoformate (8.5 mL), NaH (50∼60% in oil, 60 mg (12.5 mmol) with a content of 55%) was added at room temperature. The reaction mixture gradually dissolved and its color changed from yellow to red. The stirring was continued at room temperature for 4 h. After confirming that the reaction was complete by the disappearance of **7** by silica gel TLC (5:2:0.5 toluene–EtOAc–AcOH), the red-colored reaction mixture was poured into 15 mL of ice-cold 2 M HCI solution, and extracted twice with EtOAc. The combined extract was washed with brine and then dried over anhydrous Na_2SO_4. After removing the organic solvents in vacuo, the residual solid was recrystallized from MeOH to give **14** (55.2 mg, 91%) as a reddish orange powder.

Mp 230–240 °C (dec) (lit.[11C] 230 °C (dec)). Silica gel TLC: R_f 0.56 (5:2:0.5 toluene–EtOAc–AcOH). HPLC: t_R 8.82 min (8:2 MeOH–25% AcOH aqueous solution). UV–vis (EtOH) λ_{max} (log ε) 241 (4.37), 373 (4.57), 535 (4.95) nm; carthamin (**5**): lit.[8b] EtOH λ_{max} (log ε) 244 (4.13), 377 (4.28), 515 (4.69) nm. IR (KBr) ν 3288, 2985, 1622, 1599, 1581, 1513, 1412 cm^{-1}. ^{1}H NMR (C_5D_5N) δ 1.73 (1H, s, $CH_3\times4$), 7.71 (4H, d, $J=8.7$ Hz, *p*-substituted ArH×4), 7.81 (4H, d, $J=8.7$ Hz, *p*-substituted ArH×4), 8.23 (2H, d, $J=15.4$ Hz, *trans*-vinyl H×2), 8.72 (2H, d, $J=15.4$ Hz, *trans*-vinyl H×2), 8.94 (1H, s, =CH–). ^{13}C NMR (C_5D_5N, at 60 °C) δ 22.8 and 23.0 (CH_3,×4), 52.5 (C4), 107.5 and 115.1 (C2, 6), 117.1 (C12), 120.4 and 120.6 (C8), 127.2 (C10), 131.5 and 131.8 (C11), 145.9 (C9), 147.1 (C14), 162.3 (C13), 185.2 (C7), 187.3, 188.1, 198.7 (C1, 3, 5). FAB-MS (thioglycerol, negative ion, *m/z*) 609 $(M-H)^-$. Anal. Calcd for $C_{35}H_{30}O_{10}$ $0.1H_2O$: C, 68.64; H, 4.97. Found: C, 68.43; H, 4.90.

4.6. Conversion reaction of 12 to 14 via oxidative decarboxylation using an aqueous permanganate solution.[5b]

To a stirred solution of **12** (45 mg, 0.0686 mmol) in acetone (1.5 mL), a 0.23% aqueous solution of potassium permanganate (1.8 mL) was added in small portions over a period of 1.5 h at room temperature, and the stirring was continued for an additional 0.5 h. After confirming the disappearance of **12**, the reaction mixture was added to a 1 M HCI solution (10 mL) and then extracted twice with EtOAc. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and then evaporated in vacuo. The residue was purified by flash column chromatography on silica

gel (6:1:0.1 toluene–EtOAc–AcOH) to give **14** (21.8 mg, 52%) as a reddish orange powder.

4.7. Synthesis of the analog (8) of safflower yellow B (1)

4.7.1. 1-Deoxy-1,1-bis[3′-(*p*-hydroxycinnamoyl)filicinic acid-5′-yl]-2,3,4,5,6-penta-*O*-acetyl-D-glucitol (21). To a stirred suspension of **7** (107 mg, 0.356 mmol) in dry methanol (1.5 mL), a 28% NaOMe methanol solution was added dropwise until **7** dissolved. To the stirred mixture, 2,3,4,5,6-penta-*O*-acetyl-D-aldehydo-glucose (161 mg, 0.356 mmol) was added in small portions over a period of 3 h and then stirred at room temperature for 8 h. The progress of the reaction was monitored by silica gel TLC (5:2:0.5 toluene–EtOAc–AcOH). The reaction mixture was poured into 20 mL of ice-cold 2 M HCl and extracted three times with EtOAc. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4, and the solution evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (6:1:0.1 and 5:2:0.2 toluene–EtOAc–AcOH) to give **7** (14.5 mg, 14%), **21** (67 mg, 39%), and its mono- and di-de-*O*-acetates (71 mg, 42–45%) as a yellow powder, respectively.

Data for **21**. Mp 140–143 °C. Silica gel TLC: R_f 0.47 (5:2:0.5 toluene–EtOAc–AcOH). HPLC: t_R 16.92 min (90:10 MeOH–25% AcOH aqueous solution). IR (KBr) ν 3417, 2995, 2937, 2885, 1751, 1620, 1601, 1516, 1416, 1217 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.16, 1.17, 1.20, 1.32 (each 3H, s, $CH_3\times4$), 1.85, 1.94, 1.96, 1.96, 2.05 (each 3H, s, OAc×5), 4.19 (2H, d, $J=4.9$ Hz, H-6′a,b), 4.98 (1H, dd, $J=4.4$, 4.9 Hz, H-5′), 4.98 (1H, br. d, $J=8.5$ Hz, H-3′), 5.19 (IH, dd, $J=8.5$, 4.4 Hz, H-4′), 5.31 (1H, d, $J=10.7$ Hz, H-2′), 6.28 (1H, br. d, $J=10.7$ Hz,H-2′), 6.82 (2H, d, $J=$ 8.8 Hz, *p*-substituted ArH×2), 6.83 (2H, d, $J=8.3$ Hz, *p*-substituted ArH×2), 7.50 (2H, d, $J=8.8$ Hz, *p*-substituted ArH×2), 7.53 (2H, d, $J=8.3$ Hz, *p*-substituted ArH×2), 7.61 (1H, d, $J=15.6$ Hz, *trans*-vinyl H), 7.71 (1H, d, $J=$ 15.6 Hz, *trans*-vinyl H), 8.06 (2H, $J=15.6$ Hz, *trans*-vinyl H), 10.5 (2H, br. s, OH×2), 19.4, 19.6 (each 1H, s, OH×2). ^1H NMR (C_5D_5N) δ 1.62, 1.75, 1.82, 1.92 (each 3H, s, $CH_3\times4$), 2.02, 2.08, 2.13, 2.16, 2.23 (each 3H, s, OAc×5), 4.83 (1H, dd, $J=8.1$, 11.9 Hz, H-6a) 4.94 (1H, dd, $J=2.6$, 11.9 Hz, H-6b), 5.85 (1H, ddd $J=2.6$, 4.3, 8.1 Hz, H-5), 5.93 (1H, dd, $J=1.3$, 8.5 Hz, H-3), 6.10 (1H, dd, $J=4.3$, 8.5 Hz, H-4), 6.49 (1H, d, $J=11.1$ Hz, H-1), 7.06, 7.09 (each 1H, d, $J=9.0$ Hz, *p*-substituted ArH×2), 7.32 (1H, dd, $J=1.2$, 11.1 Hz, H-2), 7.58, 7.65 (each 2H, d, $J=9.0$ Hz, *p*-substituted ArH×4), 8.09, 8.21 (each 1H, d, $J=15.8$ Hz, *trans*-vinyl H×2), 8.87, 8.88 (each 1H, *trans*-vinyl H×2), 17.56 (1H, br. s, chelated OH). ^{13}C NMR (C_5D_5N) δ 20.5, 20.7, 20.9, 21.1, 21.4 ($COCH_3\times5$), 29.4 (C1′) 51.3 and 52.6 (C4), 61.7 (C6′), 70.7, 71.0, 71.2, 71.5 (C2′ 3′, 4′, 5′) 105.3 and 105.8 (C2), 106.0 and 106.8 (C6), 116.7 and 116.8 (C12), 122.6 and 125.6 (C8), 128.7 and 129.4 (C10), 130.7 and 130.9 (C11), 141.4 and 142.6 (C9), 160.9 and 161.2 (C13) 170.1, 170.2 170.4, 170.7, and 170.9 ($COCH_3\times5$), 173.4 (C7), 186.1 and 186.8, 189.0 and 190.1, 199.2 and 200.1 (C1, 3, 5). FAB-MS (NBA, *m/z*) 973 $(M+H)^+$. Anal. Calcd for $C_{50}H_{52}O_{20}$: C, 61.72; H, 5.39. Found: C, 61.79; H, 5.53.

4.7.2. Deoxy-1,1-bis[3′-(*p*-hydroxycinnamoyl)filicinic acid-5′-yl]-D-glucitol (8). To a solution of acetate **21** (67 mg), and its mono- and di-de-*O*-acetates (71 mg) in dry MeOH (2 mL) was added dropwise 0.44 mL of a 28% NaOMe methanol solution followed by stirring at room temperature for 1 h. After confirming the completion of the de-*O*-acetylation by silica get TLC (5:4:1 toluene–ethyl formate–formic acid), the reaction mixture was neutralized by the addition of Dowex 50 W (H^+) resin, and then filtered and washed with methanol. The filtrate was evaporated in vacuo and then purified by column chromatography on silica get (5:4:1 toluene–ethyl formate–formic acid) and then Sephadex LH-20 gel (MeOH) to give **9** (193 mg, 71% from **7**) as an orange powder.

Mp 173–176 °C. $[\alpha]_D^{22}$ +101 (*c* 0.55, MeOH). HPLC: t_R 5.03 min (80:20 MeOH–25% AcOH aqueous solution). UV–vis (EtOH) λ_{max} (log ε) 218 (4.53), 403 (4.67) nm; safflower yellow B (**1**): lit.[8b] MeOH A_{max} (log ε) 239 (4.43), 410 (4.77) nm. IR (KBr) ν 3392, 2981, 2939, 1622, 1601, 1516, 1471, 1437, 1277, 1244, 1167 cm^{-1}. ^1H NMR (C_5D_5N-CD_3OD 98:2, 60 °C) δ 1.47, 1.62, 1.68, 1.72 (each 3H, s, $CH_3\times4$), 4.31 (1H, dd, $J=4.6$, 11.5 Hz, H-6a), 4.36 (2H, dd, $J=4.1$, 5 Hz, H-6b), 4.36 (1H, m, H-5), 4.54 (1H, d, $J=8.5$ Hz, H-4), 4.73 (1H, d, $J=7.0$ Hz, H-3), 5.61 (1H, d, $J=7.0$ Hz, H-1), 5.73 (1H, t, $J=7.0$ Hz, H-2), 7.59 and 7.61 (each 2H, d, $J=8.5$ Hz, *p*-substituted ArH×4), 7.03, 7.04 (each 2H, d, $J=8.5$ Hz, *p*-substituted ArH×4), 8.03, 8.04 (each 1H, d, $J=15.6$ Hz, *trans*-vinyl H×2), 8.55, 8.83 (each 2H, d, $J=15.6$ Hz, *trans*-vinyl H×2). ^{13}C NMR (C_5D_5N-CD_3OD 98:2, 80 °C) δ 23.6, 23.9, 24.4, and 25.2 ($CH_3\times4$), 38.2 and 38.4 (C1′), 46.2 and 53.3 (C4), 64.3 (C6′), 70.8, 72.6 and 72.8 (two peaks), 73.0 and 73.1 (two peaks), 93.8 (C2′, 3′, 4′, 5′) 104.7, 105.2, 106.7, and 111.5 (C2, 6), 116.5 and 116.6 (C12), 120.6 and 121.2 (C8), 127.6 and 128.6 (C10), 130.3 and 131.0 (C11), 139.9 and 143.8 (C9), 160.0 and 161.01 (C13), 179.3 (C7), 184.0 and 185.3, 185.8 and 187.6, 199.5 and 200.3 (C1, 3, 5). FAB-MS (glycerol, negative ion, *m/z*) 761 $(M-H)^-$. Anal. Calcd for $C_{40}H_{42}O_{15}$ C.62.25; 5; H, 5.62. Found: C, 62.08; H, 5.65.

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