Synthesis of Model Compounds of Safflomin C

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3-[3,3-Dimethyl- and 3-hydroxy-3-methyl-2,4-dihydroxy-5-(4-hydroxycinnamoyl)-6-oxo-1,4-cyclohexadienyl]-3-(4-hydroxyphenyl)propanoic acid were synthesized as model compounds of safflomin C. Their spectra closely resembled that of safflomin C.

Recently we reported the structure of safflomin C (**1**), a yellow constituent of the flowers of safflower (*Carthamus tinctorius* L.),[1] and the synthesis of the methylated form of the aglycone of **1**.[2] Here we wish to report the synthesis of two model compounds of **1**, 3-[3,3-dimethyl- and 3-hydroxy-3-methyl-2,4-dihydroxy-5-(4-hydroxycinnamoyl)-6-oxo-1,4-cyclohexadienyl]-3-(4-hydroxyphenyl)propanoic acid, (**2** and **3**), as a preliminary step toward the total synthesis of **1** (Scheme 1).

First, compound **2** was synthesized by the following method (Scheme 2).

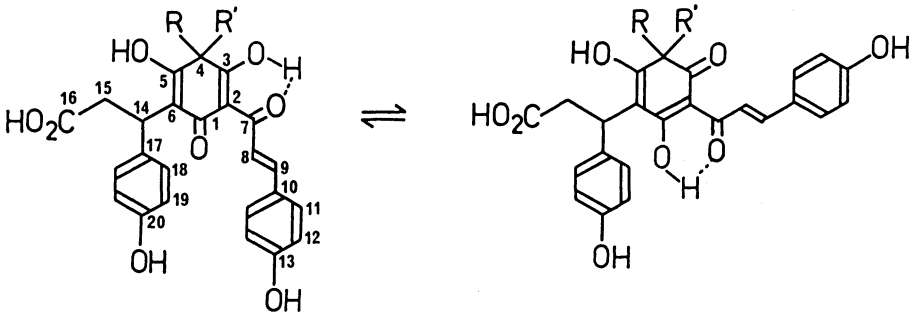
The Friedel–Crafts reaction of 2′,4′,6′-trihydroxyacetophenone (**4**) with 4-hydroxycinnamic acid in 85% phosphoric acid afforded a mixture of dihydrocoumarin derivatives, **5a** and **5b**, in 82% yield. The mixture of **5a** and **5b** was methylated with methyl iodide in the presence of sodium methoxide in methanol to give the same methylated compound, methyl 3-(5-acetyl-2,4-dihydroxy-3,3-dimethyl-6-oxo-1,4-cyclohexadienyl)-3-(4-hydroxyphenyl)propanoate (**6**), in 82% yield. Condensation of methyl 3-(5-acetyl-4-hydroxy-2-methoxy-3,3-dimethyl-6-oxo-1,4-cyclohexadienyl)-3-(4-hydroxyphenyl)propanoate (**7**), prepared by methylation of **6** with diazomethane, with *p*-hydroxybenzaldehyde in piperidine gave **8** in 33% yield. Hydrolysis of **8** with dilute HCl in methanol gave a mixture of **9a** and **9b** in 87% yield. The first target compound **2** was obtained by saponification of the mixture of **9a** and **9b** with a 2 M NaOH aqueous solution (1 M=1 mol dm^{-3}) in 55% yield.

Compound **2** was also obtained from **6** by the following method (Scheme 3).

Condensation of **6** with *p*-hydroxybenzaldehyde in piperidine gave the corresponding lactone derivative **10** in 15% yield. Compound **2** was obtained by hydrolysis of **10** with a 2 M NaOH aqueous solution in 70% yield. This model compound **2** was very unstable and partially lactonized during purification.

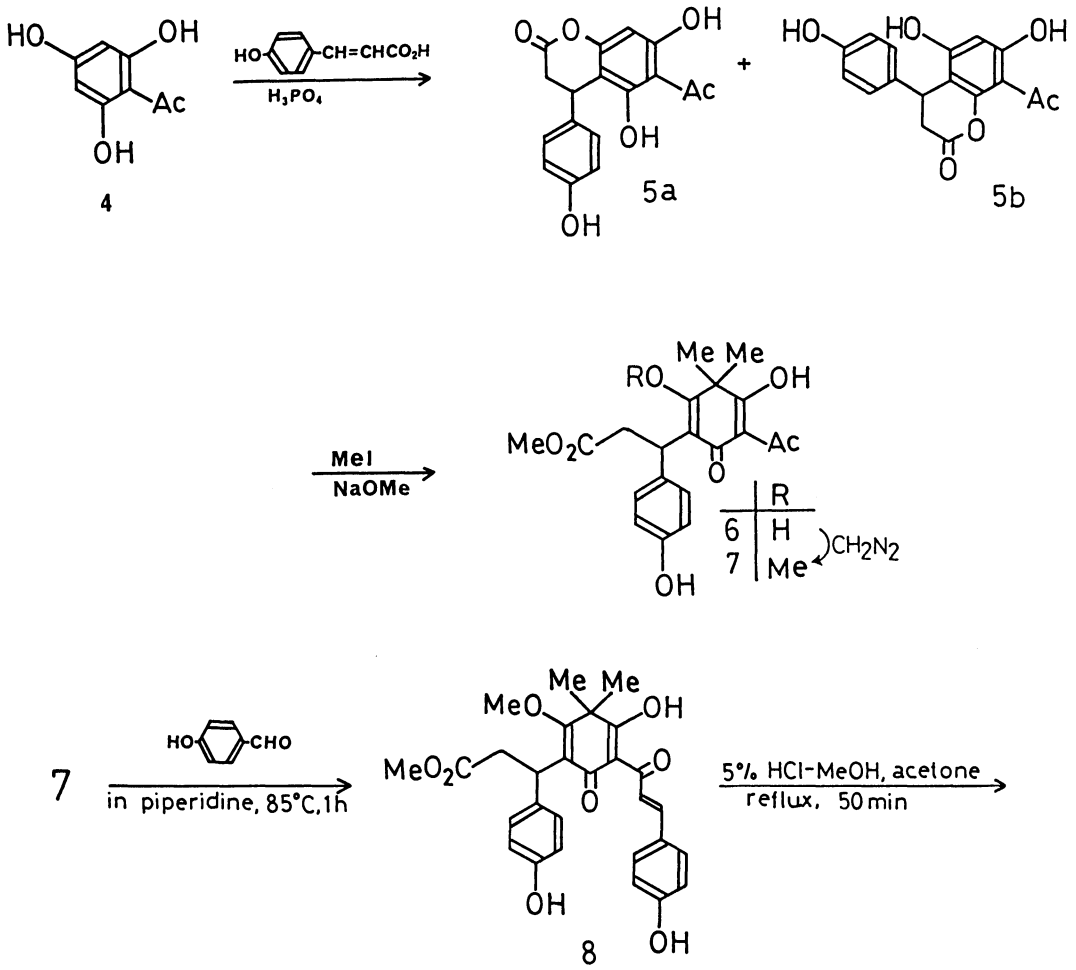
Next, compound **3** was synthesized by the following method (Scheme 4).

The Friedel–Crafts reaction of 2′,4′,6′,-trihydroxy-3′-methylacetophenone (**11**), prepared by the partial Clemmensen reduction of 3′-formyl-2′,4′,6′,-trihydroxyacetophenone, with 4-hydroxycinnamic acid afforded dihydrocoumarin derivatives (**12a** and **12b**) in 97% yield, as in the preparation of **5**. The mixture of compounds **12a** and **12b** was oxidized under air in the presence of lead(II) acetate in methanol[3] followed by methylation with diazomethane to give methyl 3-(5-acetyl-3,4-dihydroxy-2-methoxy-3-methyl-6-oxo-1,4-cyclohexadienyl)-3-(4-hydroxyphenyl)propanoate (**14**) in 63% yield. Condensation of **14** with *p*-hydroxybenz-

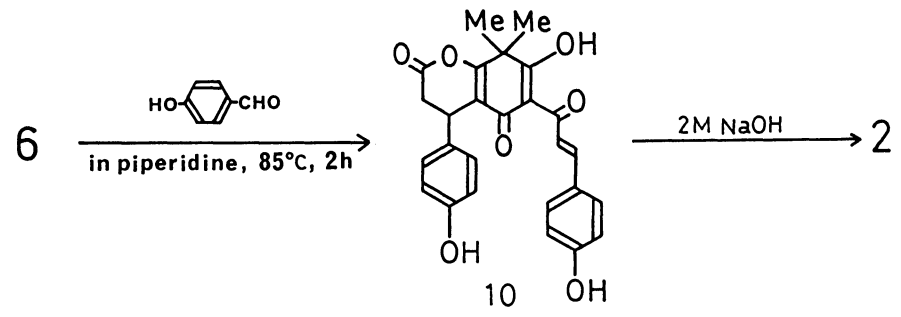


	R	R′
1	OH	D-Glucopyranosyl
2	CH_3	CH_3
3	OH	CH_3

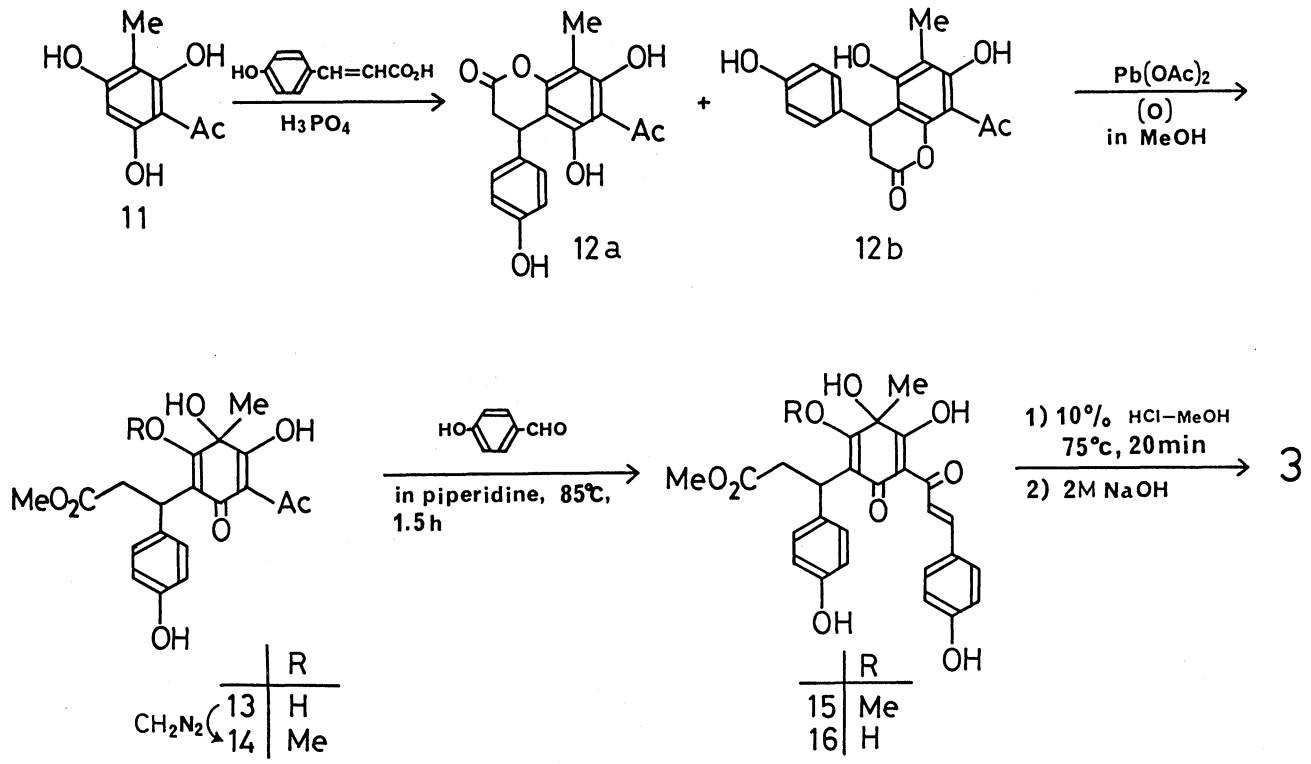
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

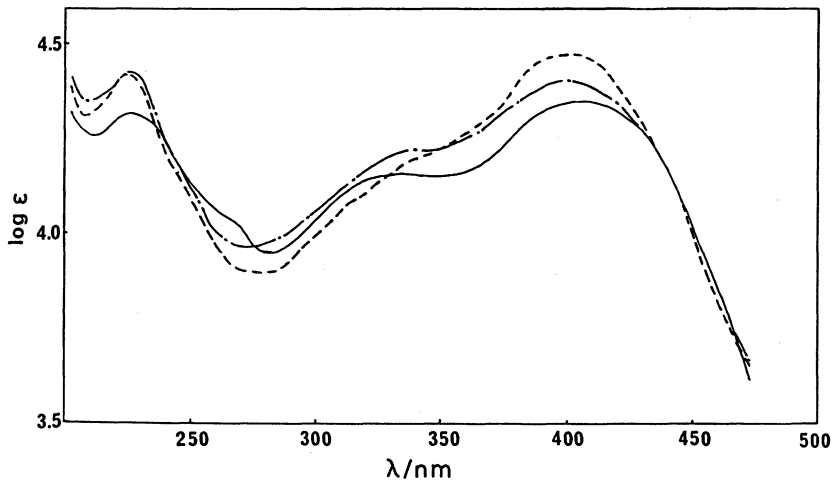


Fig. 1. Electronic spectra of safflomin C (—), and model compounds **2** (---) and **3** (-·-) in ethanol.

aldehyde in piperidine gave a mixture of **15** and **16** in a total yield of 41%. Compound **15** was quantitatively hydrolyzed with 10% HCl in methanol to give **16**. The second target compound **3** was obtained quantitatively by saponification of **16** with a 5% NaOH aqueous solution. Compound **3** was more stable and harder to be lactonized than **2**. Although the existence of two diastereomers is assumed in **3**, the stereochemistry of **3** has not been resolved yet.

The electronic spectra of compounds **2** and **3** were very similar to that of safflomin C[4] as shown in Fig. 1. The ^{13}C NMR spectra of **2** and **3** were also very similar to that of **1** excepting the sugar moiety as seen in Table 1.

These results indicate that the present method is effective to construct the skeleton of safflomin C (**1**).

Experimental

All the melting points were uncorrected. IR spectra were recorded with a Hitachi 100-50 spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a Hitachi R-600 and a

Table 1. ^{13}C NMR (DMSO-d_6) Data for Model Compound **2**, **3**, and Safflomin C[a)]

Carbon No.	2	3	Safflomin C
1	186.60 (s)	190.16 (s)	190.87 (s)
2	103.91 (s)	104.34 (s)	107.97 (s)
3	184.65 (s)	189.86 (s)	178.92 (s)
4	50.05 (s)	75.06 (s)	81.43 (s)
5	173.85 (s)	173.91 (s)	174.22 (s)
6	109.41 (s)	110.56 (s)	111.46 (s)
7	197.25 (s)	195.62 (s)	193.87 (s)
8	121.02 (d)	118.30 (d)	118.93 (d)
9	141.60 (d)	133.18 (d)	141.01 (d)
10	134.29 (s)	125.71 (s)	126.46 (s)
11	130.12 (d)[b)]	127.84 (d)[b)]	128.40 (d)[b)]
12	115.89 (d)[b)]	114.52 (d)[b)]	114.80 (d)[b)]
13	159.63 (s)	160.07 (s)	160.16 (s)
14	34.03 (d)	34.18 (d)	35.04 (d)
15	37.42 (t)	37.99 (t)[c)]	39.75 (t)
16	181.70 (s)	173.30 (s)	173.87 (s)
17	126.34 (s)	130.40 (s)	134.12 (s)
18	127.99 (d)[b)]	127.93 (d)[b)]	130.74 (d)[b)]
19	114.23 (d)[b)]	115.95 (d)[b)]	116.09 (d)[b)]
20	154.87 (s)	155.04 (s)	155.66 (s)
Methyl	24.22 (q)	28.23 (q)	
	24.09 (q)		

a) The microwave frequency was 50 MHz for compound **2** and safflomin C, and 25 MHz for compound **3**. b) These assignments may be reversed. c) This signal was detected in acetone-d_6, because the signal of methylene carbon (C15) was overlapped with those of DMSO-d_6.

Varian XL-200 spectrometers using tetramethylsilane as an internal standard. Mass spectra were obtained on a Hitachi RMU-6M and a JEOL HX-110 mass spectrometers.

6-Acetyl- and 8-Acetyl-3,4-dihydro-5,7-dihydroxy-4-(4-hydroxyphenyl)coumarin (5a,5b). A mixed solution of 2′,4′,6′-trihydroxyacetophenone (**4**, 5.0 g, 29.7 mmol) and 4-hydroxycinnamic acid (4.88 g, 29.7 mmol) in 85% phosphoric acid (80 ml) was stirred for 3 d at room temperature. The reaction mixture was poured into 5% HCl and extracted with ethyl acetate. The extract was washed with water, then with brine, and dried over Na_2SO_4 and evaporated in vacuo to give a mixture of **5a** and **5b** (7.65 g, 82%) as crude crystals, which were then recrystallized from ethyl acetate–toluene as white prisms. Mp 260 °C; MS *m/z* 314 (M^+); IR (KBr) 1835 cm^{-1} (lactone C=O); ^1H NMR (DMSO-d_6) δ=2.67 (3H, s, $-COCH_3$), 3.20 (2H, m, $-CH_2-$), 4.45 (1H, dd, *J*=6.3, and 3.0 Hz, >CH–), 6.25 (1H, s, ArH), 6.70 and 6.90 (each 2H, d, *J*=9.0 Hz, *p*-substituted ArH), 9.29 (1H, s, –OH), −11.20 (br. s) and −11.28 (br. s) (1 : 1, 1H, –OH), −13.10 (br. s) and −13.20 (br. s) (1 : 1, 1H, –OH, contributions from isomers). Found: C, 65.19; H, 4.51%. Calcd for $C_{17}H_{14}O_6$: C, 64.97; H, 4.49%.

Methyl 3-(5-Acetyl-2,4-dihydroxy-3,3-dimethyl-6-oxo-1,4-cyclohexadienyl)-3-(4-hydroxyphenyl)propanoate (6). To a stirred solution of **5a** and **5b** (1.57 g, 5 mmol), and 28% sodium methoxide solution (1.48 g, 25 mmol) in dry methanol (60 ml), methyl iodide (2.13 g, 15 mmol) was added slowly and then stirred for 1.5 h at room temperature. Methanol was evaporated in vacuo and the residue was acidified with 5% HCl and extracted with ethyl acetate. The extract was washed with water and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was chromatographed on silica gel with toluene–ethyl acetate–acetic acid (80 : 20 : 1) to give **6** (1.53 g, 82%) as crude crystals, which were then recrystallized from ethyl acetate–toluene as white prisms. Mp 140—142 °C; MS *m/z* 374 (M^+); IR (KBr) 1705 cm^{-1} (ester C=O); ^1H NMR ($CDCl_3$) δ=1.38 and 1.45 (each 3H, s, $-CH_3\times2$), 2.56 (3H, s, $-COCH_3$), 3.30 (2H, m, $-CH_2-$), 3.75 (3H, s, $-COOCH_3$), 4.65 (1H, t, *J*=9.0 Hz, >CH–), 6.79 and 7.13 (each 2H, d, *J*=8.4 Hz, *p*-substituted ArH), −18.90 (1H, br. s, chelated OH). Found: C, 64.01; H, 6.06%. Calcd for $C_{20}H_{22}O_7$: C, 64.16; H, 5.92%.

Methyl 3-(5-Acetyl-4-hydroxy-2-methoxy-3,3-dimethyl-6-oxo-1,4-cyclohexadienyl)-3-(4-hydroxyphenyl)propanoate (7). Treatment of **6** (2.0 g, 5.34 mmol) with diazomethane–ether solution gave **7** (2.07 g, 100%) as crude crystals, which were recrystallized from ethyl acetate as colorless prisms. Mp 116—117 °C; MS *m/z* 388 (M^+); IR (KBr) 1740 (ester C=O), 1630 and 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.40 (s) and 1.50 (s) (3.1 : 1, 6H, $-CH_3\times2$), 2.59 (s) and 2.63 (s) (2.2 : 1, 3H, $-COCH_3$), 3.27 (2H, br. d, *J*=8.5 Hz, $-CH_2-$), 3.66 (3H, s, $-COOCH_3$), 3.83 (s) and 3.89 (s) (1 : 2.7, 3H, $-OCH_3$), 4.71 (1H, t, *J*=8.5 Hz, >CH–), 6.72 and 7.12 (each 2H, d, *J*=9.0 Hz, *p*-substituted ArH), −18.55 (s) and −18.95 (s) (1 : 2.4, 1H, chelated OH, contributions from tautomers). Found: C, 64.93; H, 6.39%. Calcd for $C_{21}H_{24}O_7$: C, 64.94; H, 6.23%.

Methyl 3-[4-Hydroxy-5-(4-hydroxycinnamoyl)-2-methoxy-3,3-dimethyl-6-oxo-1,4-cyclohexadienyl]-3-(4-hydroxyphenyl)propanoate (8). A mixture of **7** (776 mg, 2.0 mmol) and *p*-hydroxybenzaldehyde (732 mg, 6.0 mmol) in piperidine (6 ml) was stirred at 85 °C for 1 h. The reaction mixture was cooled and acidified with 2 M HCl to give yellow precipitates, which were extracted with ethyl acetate. The extract was washed with water and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was chromatographed on silica gel with toluene–ethyl acetate–acetic acid (100 : 10 : 2.5, 100 : 20 : 5, and 100 : 40 : 5, a stepwise gradient elution) to give **8** as yellow crystals (325 mg, 33%), which were then recrystallized from ethyl acetate as yellow prisms. Mp 243—244 °C; MS *m/z* 492 (M^+); IR (KBr) 3430, 1700 (ester C=O), 1630, 1620, and 1590 cm^{-1}; ^1H NMR (DMSO-d_6) δ=1.37 (s) and 1.45 (s) (2.7 : 1, 6H, $-CH_3\times2$), 3.19 (2H, dd, *J*=7.0 and 5.0 Hz, $-CH_2-$), 3.58 (3H, s, $-COOCH_3$), 3.77 (s) and 3.85 (s) (1 : 2.7, 3H, $-OCH_3$, contributions from tautomers), 4.64 (1H, br. t, *J*=7.0 Hz, >CH–), 6.68 and 7.09 (each 2H, d, *J*=8.0 Hz, *p*-substituted ArH), 6.89 and 7.59 (each 2H, d, *J*=8.0 Hz, *p*-substituted ArH), 7.95 and 7.98 (each 1H, d, *J*=16 Hz, *trans*-CH=CH–), 9.19 and 10.24 (each 1H, s, –OH), −18.93 (1H, br. s, chelated OH). Found: C, 68.03; H, 5.84%. Calcd for $C_{28}H_{28}O_8$: C, 68.28; H, 5.73%.

Methyl 3-[2,4-Dihydroxy-5-(4-hydroxycinnamoyl)-3,3-dimethyl-6-oxo-1,4-cyclohexadienyl]-3-(4-hydroxyphenyl)-propanoate (9a) and 7-Hydroxy-2-(4-hydroxyphenyl)-6-[1-(4-hydroxyphenyl)-2-methoxycarbonylethyl]-8,8-dimethyl-3,4-dihydro-2*H*-1-benzopyran-4,5(8*H*)-dione (9b). To a stirred solution of **8** (210 mg, 0.427 mmol) in methanol (20 ml) and acetone (10 ml) was added concd HCl (6 ml). The mixture was refluxed for 50 min. After cooling, organic solvents in the reaction mixture were evaporated in vacuo. The residual suspension solution was extracted twice with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was chromatographed on silica gel with toluene–ethyl acetate–acetic acid (100 : 10 : 2.5 and 100 : 20 : 5) to give a mixture of **9a** and **9b** (184 mg, 90%), which were separated by TOYOPEARL HW-40F gel column chromatography with 80% aqueous methanol to give **9a** (55

mg, 27%) and **9b** (123 mg, 60%) as yellow and pale yellow powder, respectively. Compound **9a** was crystallized from ethyl acetate–toluene as yellow prisms: $FeCl_3$ (brown); mp 204—205 °C; MS *m/z* 478 (M^+); IR (KBr) 3450, 1720 (ester C=O), 1620, and 1595 cm^{-1}; ^1H NMR (acetone-d_6) δ=1.30 (s) and 1.45 (s) (1 : 1, 6H, $-CH_3\times2$), 3.21 (2H, d, *J*=8.0 Hz, $-CH_2-$), 3.52 (s) and 3.59 (s)(1 : 1.5, 3H, $-COOCH_3$, contributions from tautomers), 4.86 (1H, t, *J*=8.0 Hz, >CH–), 6.94 and 7.21 (each 2H, d, *J*=8.5 Hz, *p*-substituted ArH), 6.94 and 7.60 (each 2H, d, *J*=8.5 Hz, *p*-substituted ArH), 7.95 and 8.14 (each 1H, d, *J*=16 Hz, *trans*–CH=CH–), −19.31 (1H, br. s, chelated OH). Found: C, 67.45; H, 5.31%. Calcd for $C_{27}H_{26}O_8$: C, 67.77; H, 5.48%.

9b: $FeCl_3$ (dark blue); mp 109—111 °C; MS *m/z* 478 (M^+), UV (EtOH) 224 (ε 29500), 286 (sh, 10800), 313 (15600), and 366 (sh, 8000) nm; IR (KBr) 3350, 1710 (ester C=O), and 1600 cm^{-1}; ^1H NMR (acetone-d_6) δ=1.30 (6H, br. s, $-CH_3\times2$), 2.8—3.4 (4H, m, $-CH_2-\times2$), 3.54 (3H, s, $-COOCH_3$), 4.77 (1H, br. t, *J*=8.3 Hz, >CH–), 5.40 (1H, m, >CH–), 6.72 and 7.39 (each 2H, d, *J*=8.0 Hz, *p*-substituted ArH), 6.99 and 7.07 (each 2H, d, *J*=8.0 Hz, *p*-substituted ArH), 8.0 and 8.6 (each 1H, br. s, –OH). Found: C, 67.45; H, 5.31%. Calcd for $C_{27}H_{26}O_8$: C, 67.77; H, 5.48%.

3,4-Dihydro-7-hydroxy-6-(4-hydroxycinnamoyl)-4-(4-hydroxyphenyl)-8,8-dimethyl-5-oxocoumarin (10). A mixture of **6** (300 mg, 0.802 mmol) and *p*-hydroxybenzaldehyde (488 mg, 4.00 mmol) in piperidine (3.0 ml) was stirred at 85 °C for 2 h. The reaction mixture was cooled and acidified with 2 M HCl to give yellow precipitates, which were extracted with ethyl acetate. The extract was washed with water and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was chromatographed on silica gel with toluene–ethyl acetate–acetic acid (100 : 10 : 2.5 and 100 : 20 : 5) to give **10** as crude crystals (53.7 mg, 15%), which were then recrystallized from ethyl acetate as yellow prisms. Mp 251—252 °C; MS *m/z* 446 (M^+); IR (KBr) 1805 (lactone C=O), 1780, 1620, 1600 cm^{-1}; ^1H NMR (DMSO-d_6) δ=1.44 (s), 1.50 (s) and 1.59 (s) (1.3 : 1.8 : 1, 6H, $-CH_3\times2$, contribution from tautomers), 2.8 (2H, m, $-CH_2-$), 4.32 (1H, br. d, *J*=7 Hz, >CH–) , 6.74, 7.05, 7.66, and 8.18 (each 2H, d, *J*=9.0 Hz, *p*-substituted ArH), 9.24 and 10.29 (each 1H, s, –OH), −18.5 (1H, br. s, chelated OH). Found: C, 69.62; H, 4.97%. Calcd for $C_{26}H_{22}O_7$: C, 69.95; H, 4.97%.

3-[2,4-Dihydroxy-5-(4-hydroxycinnamoyl)-3,3-dimethyl-6-oxo-1,4-cyclohexadienyl]-3-(4-hydroxyphenyl)propanoic Acid (2). A solution of **10** (100 mg, 0.224 mmol) in 2 M NaOH aqueous solution (4 ml) was stirred at room temperature for 30 min. The reaction mixture was acidified with a 6 M HCl solution to give yellow precipitates, which were extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4 and evaporated in vacuo. The residue was chromatographed on silica gel with toluene–ethyl acetate–acetic acid (100 : 40 : 10) to give **2** as a yellow powder. This product was chromatographed, to remove the resulting lactone derivative (**10**), on TOYOPEARL HW-40F with 80% aqueous methanol solution to give **2** as a yellow powder (60 mg, 58%); mp 163—165 °C; FAB MS *m/z* 465 (M+H); IR (KBr) 3100 (br.), 1702 (weak), 1607, 1598 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ=1.26 (3H, s, $-CH_3$), 1.29 (3H, s, $-CH_3$), 2.95 (1H, A of ABX, J_{AB}=15.5 Hz, J_{AX}=7.6 Hz, $-CH_2-$), 3.08 (1H, B of ABX, J_{AB}=15.5 Hz, J_{BX}=7.6 Hz, $-CH_2-$), 4.70 (1H, t, *J*=7.6 Hz, >CH–), 6.63 and 7.09 (each 2H, d, *J*=8.5 Hz, *p*-substituted ArH), 6.84 and 7.51 (each 2H, d, *J*=8.5 Hz, *p*-substituted ArH), 7.66 and 8.06 (each 1H, d, *J*=18.0 Hz, *trans* –CH=CH–), 9.06 and 10.04 (each 1H, br. s, –OH×2), −18.98 (1H, br. s, chelated OH). Found: C, 67.05; H, 5.12%. Calcd for $C_{26}H_{24}O_8$: C, 67.24; H, 5.21%.

2′,4′,6′,-Trihydroxy-3′-methylacetophenone (11). To a mixed solution of concd HCl (30 ml), water (8 ml), and zinc amalgam (110 g) in methanol (60 ml) was added 3′-formyl-2′,4′,6′,-trihydroxyacetophenon[5] (1.135 g, 5.79 mmol). The mixture was stirred at 50 °C for 15 min. The reaction mixture was filtered. To the filtrate was added water (135 ml) followed by extraction with ether. The extract was dried over Na_2SO_4 and evaporated in vacuo to give **11** as crude crystals (1.025 g, 97%), which were then recrystallized from methanol as colorless prisms; mp 209—210 °C; MS *m/z* 182 (M^+); IR (KBr) 3400 (br.), 1630 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ=1.85 (3H, s, $-CH_3$), 2.67 (3H, s, $-COCH_3$), 6.03 (1H, s, ArH), 10.26, 10.51, and 13.94 (each 1H, s, –OH). Found: C, 59.08; H, 5.62%. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53%.

6-Acetyl-3,4-dihydro-5,7-dihydroxy-8-methyl-4-(4-hydroxyphenyl)coumarin (12a) and 8-Acetyl-3,4-dihydro-5,7-dihydroxy-6-methyl-4-(4-hydroxyphenyl)coumarin (12b). A mixed solution of **11** (0.93 g, 5.11 mmol) and 4-hydroxycinnamic acid (0.83 g, 5.11 mmol) in 85% phosphoric acid (50 ml) was stirred for 2.5 d at room temperature. The reaction mixture was poured into 5% HCl and extracted with ethyl acetate. The extract was washed with water and brine, and dried over Na_2SO_4, and then evaporated in vacuo to give a mixture of **12a** and **12b** (1.63 g, 97%) as crude crystals, which were then recrystallized from ethyl acetate–toluene as pale orange crystals; mp 247—249 °C; MS *m/z* 328 (M^+); IR (KBr) 1750 cm^{-1} (lactone C=O); ^1H NMR (DMSO-d_6) δ=2.02 (s) and 2.08 (s) (1 : 1.4, 3H, $-CH_3$), 2.69 (3H, s, $-COCH_3$), 2.95—3.18 (2H, m, $-CH_2-$), 4.56 (1H, br. d, *J*=6.0 Hz, >CH–), 6.79 and 6.88 (each 2H, d, *J*=7.2 Hz, *p*-substituted ArH), −9.33 (br. s), −10.02 (br. s), −11.37 (br. s), −12.13 (br. s), and −13.87 (s) (1.7 : 1 : 1.2 : 1.4 : 3.9, 3H, –OH×3, contributions from isomers). Found: C, 65.70; H, 4.93%. Calcd for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91%.

Methyl 3-(5-Acetyl-2,3,4-trihydroxy-3-methyl-6-oxo-1,4-cyclohexadienyl)-3-(4-hydroxyphenyl)propanoate (13). A mixed solution of **12a** and **12b** (1.31 g, 3.99 mmol) and lead(II) acetate trihydrate (1.75 g) in methanol (30 ml) was stirred on exposure to air for 2.5 d at room temperature. The reaction mixture was concentrated in vacuo and acidified with dilute H_2SO_4, and extracted with ethyl acetate. The extract was washed with water and brine, dried over Na_2SO_4, and then evaporated in vacuo. The residue was chromatographed on silica gel with toluene–ethyl formate–formic acid (50 : 20 : 5) to give **13** (0.95 g, 63%) as a pale yellow viscous oil, which was then crystallized from ethyl acetate as pale yellow prisms, with recovery of **12a** and **12b** (0.35 g, 27%). Mp 177—179 °C; MS *m/z* 376 (M^+); IR (KBr) 1705 cm^{-1}(ester C=O); ^1H NMR (DMSO-d_6) δ=1.36 (3H, s, $-CH_3$), 2.44 (3H, s, $-COCH_3$), 3.08 (2H, d, *J*=8.4 Hz, $-CH_2-$), 3.53 (3H, s, $-COOCH_3$), 4.62 (1H, t, *J*=8.4 Hz, >CH–), 6.62 and 7.06 (each 2H, d, *J*=8.4 Hz, *p*-substituted ArH), −18.85 (1H, br. s, chelated OH). Found: C, 60.68; H, 5.36%. Calcd for $C_{19}H_{20}O_8$: C, 60.64; H, 5.36%.

Methyl 3-(5-Acetyl-3,4-dihydroxy-2-methoxy-3-methyl-6-oxo-1,4-cyclohexadienyl)-3-(4-hydroxyphenyl)propanoate (14). Treatment of **13** (0.82 g, 2.18 mmol) with diazomethane–ether solution gave **14** (0.82 g, 96%) as a colorless viscous oil , which was crystallized from ethyl acetate–toluene. Mp 171—172 °C (white prism); MS *m/z* 390 (M^+); IR (KBr)

1710 cm^{-1} (ester C=O); ^1H NMR ($CDCl_3$) δ=1.53 (s) and 1.57 (s) (1.2:1, 3H, $-CH_3$), 2.53 (3H, s, $-COCH_3$), 3.12 (2H, br. d, J=8.4 Hz, $-CH_2-$), 3.63 (3H, s, $-COOCH_3$), 4.16 (s) and 4.21 (s) (1:1.2, 3H, $-OCH_3$, contributions from tautomers), 4.85 (1H, t, J=8.4 Hz, >CH-), 6.72 and 7.14 (each 2H, d, J=8.4 Hz, p-substituted ArH), −18.75 (1H, br. s, chelated OH). Found: C, 61.60; H, 5.69%. Calcd for $C_{20}H_{22}O_8$: C, 61.53; H, 5.68%.

Methyl 3-[3,4-Dihydroxy-5-(4-hydroxycinnamoyl)-2-methoxy-3-methyl-6-oxo-1,4-cyclohexadienyl]-3-(4-hydroxyphenyl)propanoate (15) and Methyl 3-[2,3,4-Trihydroxy-5-(4-hydroxycinnamoyl)-3-methyl-6-oxo-1,4-cyclohexadienyl]-3-(4-hydroxyphenyl)propanoate (16). A mixed solution of **14** (0.75 g, 1.92 mmol) and p-hydroxybenzaldehyde (0.70 g, 5.76 mmol) in piperidine (8 ml) was stirred for 1.5 h at 85 °C. The reaction mixture was poured into ice-cold dilute HCl and extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was chromatographed on silica gel with toluene–ethyl acetate–acetic acid (200:80:1) to give **15** (0.190 g, 20%) and the demethylated product (**16**, 0.194 g, 21%). Compound **15** was crystallized from ethyl acetate–toluene, giving yellow prisms. To a solution of **15** (0.216 g, 0.437 mmol) in methanol (6 ml) was added concd HCl (3 ml) and then the solution was stirred at 75 °C for 20 min. After cooling, cold water was added to the reaction mixture, and extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, and then evaporated in vacuo to give **16** (0.208 g, 99%) as a yellow powder.

15: Mp 196—198 °C; MS m/z 494 (M^+); ^1H NMR ($CDCl_3$) δ=1.58 (s) and 1.61 (s) (1.2:1, 3H, $-CH_3$), 3.18 (2H, br. d, J=8 Hz, $-CH_2-$), 3.65 (3H, s, $-COOCH_3$), 4.10 (s) and 4.19 (s) (1.3:1, 3H, $-OCH_3$), 4.89 (1H, br. t, J=8 Hz, >CH-), 6.72 and 7.27 (each 2H, d, J=8.4 Hz, p-substituted ArH), 6.86 and 7.46 (each 2H, d, J=8.6 Hz, p-substituted ArH), 7.88 and 7.90 (each 1H, d, J=16.0 Hz, *trans*-CH=CH-), −18.62 (br. s) and −18.65 (br. s) (1.3:1, 1H, chelated OH, contributions from tautomers). Found: C, 65.85; H, 5.41%. Calcd for $C_{27}H_{26}O_9$: C, 65.58; H, 5.30%.

16: Mp 130—133 °C; FAB MS m/z 481 (M+H); IR (KBr) 3350 (br.), 1713 (ester C=O), 1660, 1620, 1598 cm^{-1}; ^1H NMR (acetone-d_6) δ=1.54 (s) and 1.58 (s) (1.2:1, 3H, $-CH_3$, contribution from tautomers), 3.25 (2H, br. d, J=8.5 Hz, $-CH_2-$), 3.58 (3H, s, $-COOCH_3$), 4.87 (1H, br. t, J=8.5 Hz, >CH-), 6.74 and 7.24 (each 2H, d, J=8.6 Hz, p-substituted ArH), 7.10, and 7.59 (each 2H, d, J=8.6 Hz, p-substituted ArH), 7.94 and 7.96 (each 1H, d, J=16.0 Hz, *trans*-CH=CH-), −18.99 (1H, br. s, chelated OH). Found: C, 64.83; H, 5.03%. Calcd for $C_{26}H_{24}O_9$: C, 65.00; H, 5.03%.

3-[2,3,4-Trihydroxy-5-(4-hydroxycinnamoyl)-3-methyl-6-oxo-1,4-cyclohexadienyl]-3-(4-hydroxyphenyl)propanoic Acid (3). A solution of **16** (100 mg, 0.202 mmol) in 2 M NaOH aqueous solution (3 ml) was stirred at room temperature for 0.5 h. A cold 6 M HCl solution was added to the reaction mixture in an ice bath and extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, and then evaporated in vacuo. The residue was chromatographed on silica gel with toluene–ethyl acetate–acetic acid (100:20:5 and 100:40:10) to give **3** as a crude powder (79 mg, 83%). This product was rechromatographed on TOYOPEARL HW-40F with 80% aqueous methanol solution to give **3** (68 mg, 72%) as a reddish brown powder; mp 153—156 °C; FAB MS m/z 467 (M+H); IR (KBr) 3250 (br.), 1705 (weak), 1600 cm^{-1}; ^1H NMR (200 MHz, acetone-d_6) δ=1.56 (s) and 1.58 (s) (2:1, 3H, $-CH_3$, contribution from tautomers), 3.21 (2H, d, J=8.0 Hz, $-CH_2-$), 4.82 and 4.88 (1H, each t, J=8.0 Hz, >CH-, a mixture of diastereomers, in a 1:2 ratio), 6.73 and 7.24 (each 2H, d, J=8.5 Hz, p-substituted ArH), 6.94 and 7.58 (each 2H, d, J=8.5 Hz, p-substituted ArH), 7.86 and 7.98 (each 1H, d, J=15.6 Hz, *trans*-CH=CH-), −19.03 (br. s) and −19.07 (br. s) (1.6:1, 1H, chelated OH, contribution from tautomers). Compound **3** was easily took up some solvents irreversibly, and hygroscopic. In view of this, after drying at 90 °C for 2 h, compound **3** was stored in a water-saturated atmosphere overnight and then submitted to elemental analysis. Found: C, 60.68; H, 5.48%. Calcd for $C_{25}H_{22}O_9$ 1.6 H_2O: C, 60.63; H, 5.13%.

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4) The electronic spectra of model compounds were different from that of safflomin C in a previous paper[1] between 200 and 300 nm. In the meantime we found that these compounds readily and irreversibly take up various solvents. Therefore the electronic spectrum of safflomin C re-purified by the use of aqueous acetic acid–methanol solution was conducted again, to find that it is similar to those of model compounds as seen in Fig. 1. Thus the previous electronic spectrum of safflomin C has been revised here.

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