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An Easy Two-Synthon Synthesis of a Sweet Dihydroisocoumarin, (±)-Phyllodulcin.[1] Studies on the *β*-Carbonyl Compounds Connected with *β*-Polyketides. IX[2]

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(±)-Phyllodulcin (**1**), a sweet dihydroisocoumarin of *Hydrangea serrata* SERINGE var. *thunbergii* SUGIMOTO, was synthesized by aromatic annelation of two synthons **2** and **3** to yield **5**, followed by successive debenzylation, hydrolysis, lactonization, and decarboxylation in the sequence **5**→**9**→**10**→**11**→**1**.

Keywords——(±)-phyllodulcin; sweet principle; *Hydrangea serrata*; dihydroisocoumarin; aromatic annelation

A naturally occurring dihydroisocoumarin, phyllodulcin (**1**), is well known as a sweet principle of *Hydrangea serrata* SERINGE var. *thunbergii* SUGIMOTO (Japanese name; Amacha).[3] Recently, we reported a biogentic-type synthesis of **1** modelled on the polyketide mode of biosynthesis.[4] Although chemical syntheses of **1** have already been reported,[5,6] we describe herein a new alternative synthesis by a simple and short route, applying the new aromatic annelation reaction reported in the preceding paper,[2] with enaminones and methyl 3-oxoglutarate.

The present synthetic strategy consists of aromatic annelation with two easily accessible synthons, namely, the enaminone **2** and dimethyl 3-oxoglutarate (**3**), as shown in Chart 1.

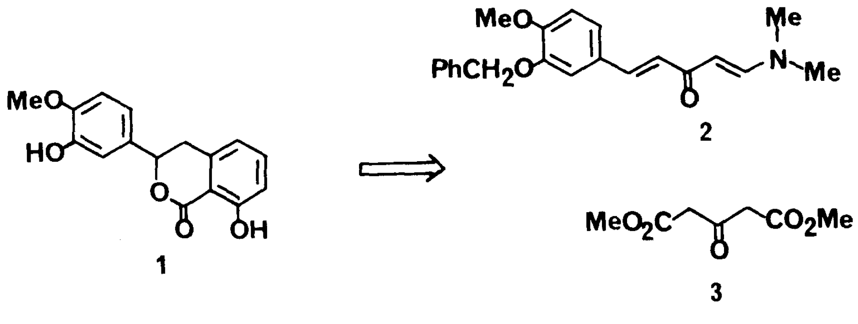

Chart 1

The enaminone **2**, 1-(3-benzyloxy-4-methoxyphenyl)-5-dimethylamino-1,4-pentadien-3-one, mp 126—128 °C, was prepared by condensing benzylisovanillin with acetone (quantitative yield) in the presence of 10% NaOH, followed by treatment (90% yield) of the resulting benzylideneacetone **4**, mp 87—89 °C, with bisdimethylaminomethoxymethane in dimethylformamide (DMF).

The reaction of **2** with **3**, catalyzed by KF–AcOH (method A) or AcONa–AcOH and 18-crown-6 (method B), afforded the condensation product **5**, mp 128—130 °C, in the yield of 61.3 or 47%. Reaction by method A was carried out by refluxing **2** (1 mol) and **3** (2 mol) in dioxane in the presence of KF and AcOH for 12 h. Reaction by method B was done by heating **2** (1 mol) and **3** (2 mol) in the presence of catalytic amounts of AcONa, AcOH, and 18-crown-6 at 70 °C in toluene for 3 h. Analytical data show that the condensation product **5** is dimethyl 4-[2-(3-benzyloxy-4-methoxyphenyl)ethenyl]-2-hydroxy-1,3-benzenedicarboxylate.

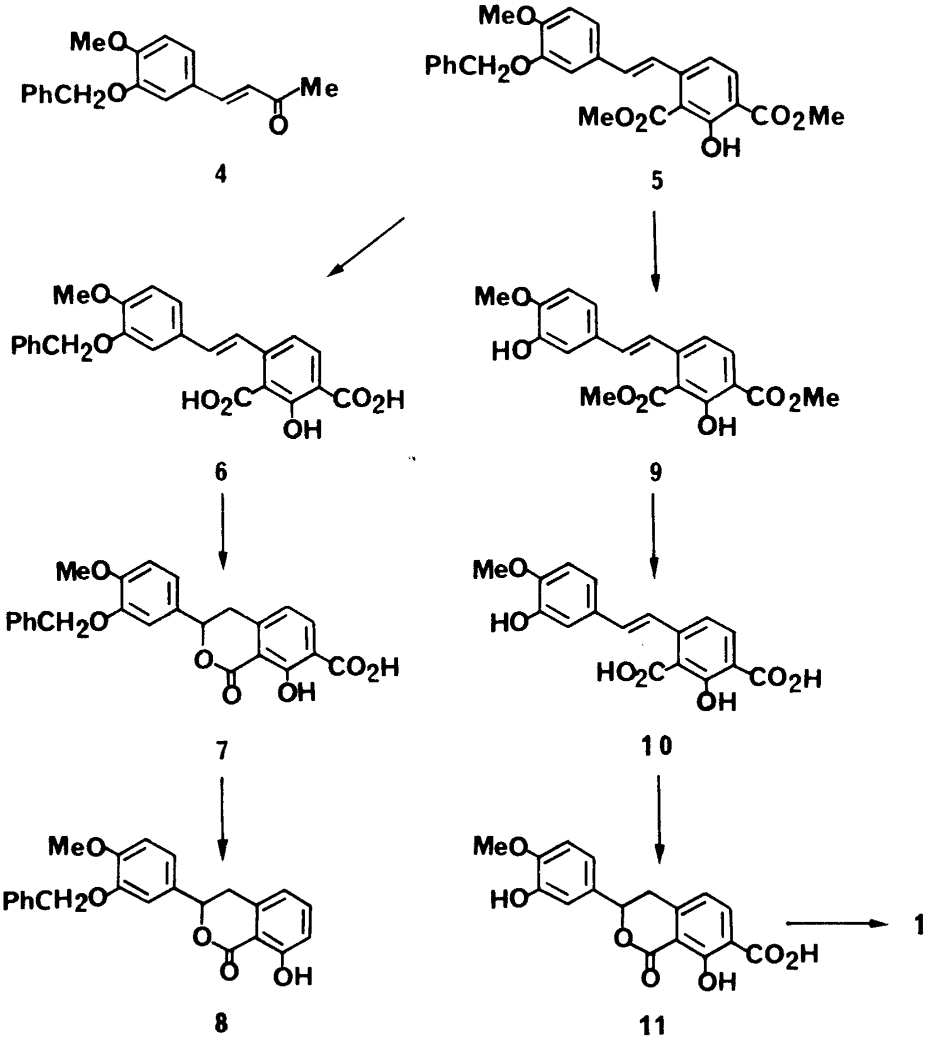

Chart 2

The diester **5** was hydrolyzed with 10% KOH in MeOH to give the acid **6**, mp 189—191 °C, in 94.7% yield. Lactonization of **6** was achieved by the treatment with CF_3CO_2H in CH_2Cl_2 at room temperature for 20 min to give the lactone **7**, mp 160—162 °C, in 69.1% yield. The lactone **7** was decarboxylated by heating it in a sealed tube in MeOH in the presence of quinoline at 180 °C for 14 h to afford benzylphyllodulcin **8**, mp 145—146 °C, (13.3% yield), which was identical with an authentic sample prepared from natural phyllodulcin. The following alternative route was investigated because of the poor yield in the above decarboxylation step.

Debenzylation of **5** with conc. HCl in MeOH afforded the diester **9**, mp 163—165 °C, in 67.5% yield. The diester **9** was hydrolyzed with 10% KOH in aqueous MeOH to give the acid **10**, mp 210—213 °C, in 97.8% yield. Lactonization of **10** was carried out by treatment with conc. H_2SO_4 at 0 °C for 10 min to afford the lactone **11**, mp 201—203 °C, in 72% yield. The lactone **11** was decarboxylated by heating it in a sealed tube in water at 180 °C for 15 h to give

(±)-phyllodulcin **1**, mp 128—130 °C, in 70% yield. All physical data for this synthetic phyllodulcin **1** were identical with those of the natural product except for its optical rotation.

This synthesis of (±)-phyllodulcin consists of seven steps, including two hydrolysis steps, from benzylisovanillin and gives an overall yield of *ca.* 19%.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were taken with a Hitachi 215 spectrometer, proton nuclear magnetic resonance (^{1}H-NMR) spectra with a Varian T-60 spectrometer at 60 MHz with tetramethylsilane as an internal standard ($CDCl_3$ and $CDCl_3$+DMSO-d_6 soln.), and mass spectrum (MS) with a Hitachi RMS-4 spectrometer at 70 eV using the direct insertion technique. Elementary analyses were done by Mrs. K. Sasaki, Kissei Pharmaceutical Company, Matsumoto, Japan. Mallinckrodt silica gel (100 mesh) and Merck Kieselgel G nach Stahl were used for column chromatography and thin-layer chromatography (TLC), respectively.

4-(3-Benzyloxy-4-methoxyphenyl)-3-buten-2-one (4)——Water (25 ml) and 10% NaOH (25 ml) were added to a solution of benzylisovanillin (50 g) in acetone (120 ml) and the whole was stirred at room temperature for 4 h. The separated crystals were collected to yield 58.2 g (99.8%) of **4** as crystals, mp 87—89 °C. IR (Nujol): 1668, 1645, 1630, 1605, 1584, 1520 cm^{-1}. NMR ($CDCl_3$) δ: 2.30 (3H, s, -COMe), 3.90 (3H, s, OMe), 5.15 (2H, s, -OCH_2Ph), 6.50 (1H, d, J=16 Hz, olefinic H), 7.10 (1H, d, J=16 Hz, olefinic H); MS *m/e*: 282 (M^+).

1-(3-Benzyloxy-4-methoxyphenyl)-5-dimethylamino-1,4-pentadien-3-one (2)——Bisdimethylaminomethoxymethane (13 g) was added to a solution of **4** (20 g) in DMF (45 ml) and the whole was heated at 80 °C for 4 h. The reaction mixture was poured into water and the separated crystals were collected to yield 21.5 g (90%) of **2** as crystals, mp 126—128 °C (benzene). IR (Nujol): 1660, 1612, 1588, 1560, 1520 cm^{-1}. NMR ($CDCl_3$) δ: 3.00 (6H, s, -NMe_2), 3.88 (3H, s, -OMe), 5.15 (2H, s, -OCH_2Ph); MS *m/e*: 337 (M^+). *Anal.* Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.89; H, 6.84; N, 3.93.

Dimethyl 4-[2-(3-Benzyloxy-4-methoxyphenyl)ethenyl]-2-hydroxy-1,3-benzenedicarboxylate (5)——Method A: Acetic acid (2.4 g) and KF (1.16 g) were added to a solution of **2** (3.39 g) and **3** (3.39 g) in dry dioxane (5 ml) and the whole was refluxed overnight. The reaction mixture was concentrated under a vacuum, acidified with 5% HCl and then extracted with chloroform. The chloroform layer was washed with sat. $NaHCO_3$ and water, dried and concentrated. The residue was recrystallized from ether–*n*-hexane to yield 2.76 g (61.3%) of **5** as crystals, mp 128—130 °C. IR (Nujol): 1713, 1660, 1620, 1589, 1510 cm^{-1}. NMR ($CDCl_3$) δ: 3.92 (3H, s, -OMe), 3.96 (6H, s, 2×OMe), 5.20 (2H, s, -OCH_2Ph), 7.80 (1H, d, J=8 Hz, aromatic H), 11.50 (1H, br, phenolic H); MS *m/e*: 448 (M^+). *Anal.* Calcd for $C_{26}H_{24}O_7$: C, 69.63; H, 5.39. Found: C, 69.34; H, 5.34.

Method B: Ac_2O (0.1 ml), AcONa (50 mg), and 18-crown-6 (100 mg) were added to a solution of **2** and **3** in benzene (10 ml) and the whole was heated at 70 °C for 12 h. The reaction mixture was worked up as described in method A and gave 251 mg (47%) of **5**.

4-[2-(3-Benzyloxy-4-methoxyphenyl)ethenyl]-2-hydroxy-1,3-benzenedicarboxylic Acid (6)——A 10% KOH solution (4 ml) was added to a solution of **5** (448 mg) in MeOH (6 ml) and the whole was refluxed for 3 h. The reaction mixture was acidified with 10% HCl and then extracted with ethyl acetate. The organic layer was extracted with sat. $NaHCO_3$ and then the aqueous layer was acidified with conc. HCl. The separated crystals were collected and recrystallized from ethyl acetate to yield 339 mg (94.7%) of **6** as crystals, mp 189—191 °C. IR (Nujol): 1660, 1610, 1505 cm^{-1}. NMR ($CDCl_3$+DMSO-d_6) δ: 3.88 (3H, s, -OMe), 5.16 (2H, s, -OCH_2Ph), 7.90 (1H, d, J=8 Hz, aromatic H); MS *m/e*: 420 (M^+).

3-(3-Benzyloxy-4-methoxyphenyl)-3,4-dihydro-8-hydroxy-7-isocoumarincarboxylic Acid (7)——CF_3CO_2H (4 ml) was added to a solution of **6** (210 mg) in CH_2Cl_2 (4 ml) and the whole was allowed to stand at room temperature for 20 min. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water, dried and concentrated. The residue was recrystallized from ethyl acetate to yield 145 mg (69.1%) of **7** as crystals, mp 160—162 °C. IR (Nujol): 1682, 1620, 1525 cm^{-1}. NMR ($CDCl_3$+DMSO-d_6) δ: 3.30 (2H, m, -CH_2-), 3.98 (3H, s, -OMe), 5.20 (2H, s, -OCH_2Ph), 5.45 (1H, q, J=5 and 9 Hz, -O-C-H), 8.15 (1H, d, J=8 Hz, aromatic H); MS *m/e*: 420 (M^+). *Anal.* Calcd for $C_{24}H_{20}O_7$: C, 69.63; H, 5.39. Found: C, 69.34; H, 5.34.

3′-*O*-Benzylphyllodulcin (8)——A small amount of quinoline was added to a solution of **7** (85 mg) in MeOH (5 ml) and the whole was heated at 180 °C in a sealed tube for 14 h. The reaction mixture was poured into water, acidified with 10% HCl and then extracted with ethyl acetate. The organic layer was washed with water, dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate yielded 10 mg (13.3%) of **8** as crystals, mp 145—146 °C (ether–*n*-hexane). IR (Nujol): 1685, 1605, 1595, 1520 cm^{-1}. NMR ($CDCl_3$) δ: 3.07 (2H, m, -CH_2-), 3.86 (3H, s, -OMe), 5.13 (2H, s, -OCH_2Ph), 5.46 (1H, dd, J=6 and 12 Hz, -O-C-H), 11.92 (1H, s, phenolic H); MS *m/e*: 376 (M^+). This compound **8** was identical with an authentic sample.[5)]

Dimethyl 2-Hydroxy-4-[2-(3-hydroxy-4-methoxyphenyl)ethenyl]-1,3-benzenedicarboxylate (9)——Conc. HCl (100 ml) was added to a solution of **5** (3.5 g) in MeOH (200 ml) and the whole was refluxed for 24 h. The reaction mixture was concentrated and allowed to stand at room temperature. The separated crystals were collected and recrystallized from ether–*n*-hexane to yield 1.89 g (67.5%) of **9** as crystals, mp 163—165 °C. IR (Nujol): 1714, 1668, 1611, 1586, 1510 cm^{-1}. NMR ($CDCl_3$) δ: 3.88 (3H, s, -OMe), 3.90 (3H, s, -OMe) 3.92 (3H, s, -OMe), 5.64 (1H, s, phenolic H), 7.80 (1H, d, $J=8$ Hz, aromatic H), 11.50 (1H, s, phenolic H); MS *m/e*: 358 (M^+).

2-Hydroxy-4-[2-(3-hydroxy-4-methoxyphenyl)ethenyl]-1,3-benzenedicarboxylic Acid (10)——A 10% KOH solution (5 ml) was added to a solution of **9** (500 mg) in EtOH (7 ml) and the whole was refluxed for 3 h. The reaction mixture was acidified with 10% HCl and extracted with ethyl acetate. The organic layer was washed with water, dried and concentrated. The residue was recrystallized from ethyl acetate to yield 451 mg (97.8%) of **10** as crystals, mp 210—213 °C. IR (Nujol): 1680, 1610, 1586, 1518 cm^{-1}. NMR ($CDCl_3+DMSO$-d_6) δ: 3.90 (3H, s, -OMe), 7.90 (1H, d, $J=8$ Hz, aromatic H); MS *m/e*: 330 (M^+). *Anal.* Calcd for $C_{17}H_{14}O_7$: C, 61.82; H, 4.27. Found: C, 61.55; H, 4.39.

3,4-Dihydro-8-hydroxy-3-(3-hydroxy-4-methoxyphenyl)-7-isocoumarincarboxylic Acid (11)——A mixture of **10** (100 mg) and conc. H_2SO_4 (0.5 ml) was stirred at 0 °C for 30 min. The reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed with water, dried and concentrated. The residue was recrystallized from MeOH to yield 72 mg (72%) of **11** as crystals, mp 201—203 °C. IR (Nujol): 1718, 1662, 1610, 1508 cm^{-1}. NMR ($CDCl_3+DMSO$-d_6) δ: 3.20 (2H, m, $-CH_2-$), 3.86 (3H, s, -OMe), 5.45 (1H, dd, $J=5$ and 9 Hz, -O-C-H), 8.05 (1H, d, $J=8$ Hz, aromatic H); MS *m/e*: 330 (M^+).

(±)-Phyllodulcin (1)——A mixture of **11** (70 mg) and dist. water (2 ml) was heated at 180 °C in a sealed tube for 15 h. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with sat. $NaHCO_3$, dried and concentrated. The residue was recrystallized from EtOH to yield 41.3 mg (70%) of **1** as crystals, mp 128—130 °C. IR (KBr): 1670, 1620, 1590, 1518 cm^{-1}. NMR ($CDCl_3+DMSO$-d_6) δ: 3.13 (2H, m, $-CH_2-$), 3.83 (3H, s, -OMe), 5.56 (1H, q, $J=5$ and 11 Hz, -O-C-H), and 10.48 (1H, s, phenolic H). This compound **1** was identical with natural (±)-phyllodulcin.

References and Notes

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