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Biogenetic-type Synthesis of (±)-Phyllodulcin, a Sweet Principle of *Hydrangea serrata* Seringe var. *thunbergii* Sugimoto[1] (Studies on the β-Carbonyl Compounds connected with the β-Polyketides. VI)[2]

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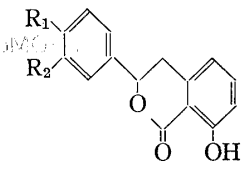
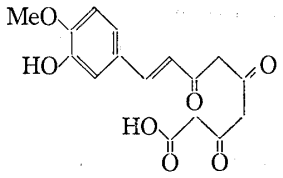
A biogenetic-type synthesis of (±)-phyllodulcin (**2**), a sweet principle of *Hydrangea serrata* Seringe var. *thunbergii* Sugimoto, from 3-(3-benzyloxy-4-methoxyphenyl)-2-propenal (**7**) modelled on the polyketide mode of biosynthesis is described.

Keywords——β-polyketides; biogenetic-type synthesis; condensation reaction; pyrones; dihydroisocoumarins; enaminoketones

In the preceding paper, we reported the biogenetic-type synthesis of a dihydroisocoumarin **1** mimicking the biosynthesis of the natural isocoumarin.[2] In this paper, we describe the synthesis of a naturally occurring dihydroisocoumarin, (±)-phyllodulcin (**2**), a sweet principle of *Hydrangea serrata* Seringe var. *thunbergii* Sugimoto (Japanese name: Amacha),[4] modelled on the polyketide mode of biosynthesis *via* the C_6–C_3–C_6 precursor **3** derived from shikimic acid and acetate (shikimate–malonate route).[5]



1: R_1=H, R_1=H
2: R_2=OMe, R_2=OH



3

Chart 1

The chosen starting material **7**, 3-(3-benzyloxy-4-methoxyphenyl)-2-propenal, was synthesized from benzylisovanillin (**4**) by the method of Isler.[6] That is, the reaction of benzylisovanillin with ethyl orthoformate in the presence of a catalytic amount of NH_4Cl in ethanol gave the acetal **5** (92.6% yield), mp 45.5—46.5°, which was transformed into the two-carbon lengthened acetal **6** (67% yield), bp 175—185° (0.8 mmHg), by condensation with ethylvinylether in the presence of $ZnCl_2$. The resulting acetal **6** was converted to the corresponding aldehyde **7** (59.6% yield), mp 83—83.5°, by hydrolysis with H_3PO_4.

The aldehyde **7** and dehydroacetic acid (**9**) were condensed in pyridine in the presence of a catalytic amount of piperidine to give the condensation product **11** (89.7% yield), mp 179—

1) For a preliminary reported of this work, see N, Takeuchi, M. Murase, K. Ochi, and S. Tobinaga, *Chem. Commun.*, **1976**, 820.
2) Part V: N. Takeuchi and S. Tobinaga, *Chem. Pharm. Bull.*, **28**, 3007 (1980).
3) Location: *Tsurumaki, Setagaya-ku, Tokyo 154, Japan.*
4) Y. Asahina and J. Asano, *Yakugaku Zasshi*, **51**, 749 (1913); *idem*, *Chem. Ber.*, **62**, 171 (1929); **63**, 429, 2049 (1930); **64**, 1252 (1931).
5) D.E. Hathway, *Biochem. J.*, **71**, 553 (1959); T.A. Geissman, "Biogenesis of Natural Compounds," ed. P. Bernfeld, Pergamon, Oxford, 1967, p. 743.
6) O. Isler, H. Lindlar, M. Montavon, R. Rüegg, and P. Zeller, *Helv. Chem. Acta.*, **39**, 249 (1956).

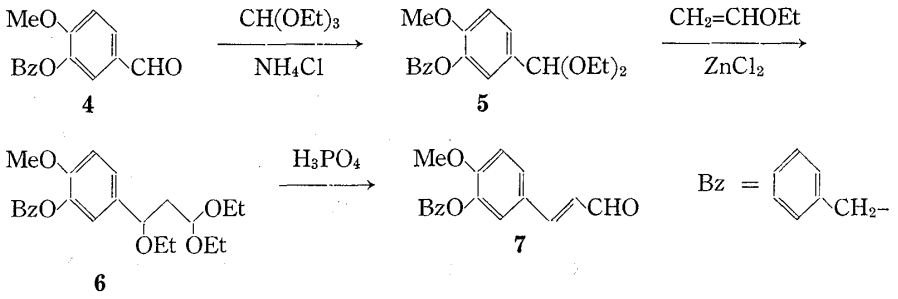


Chart 2

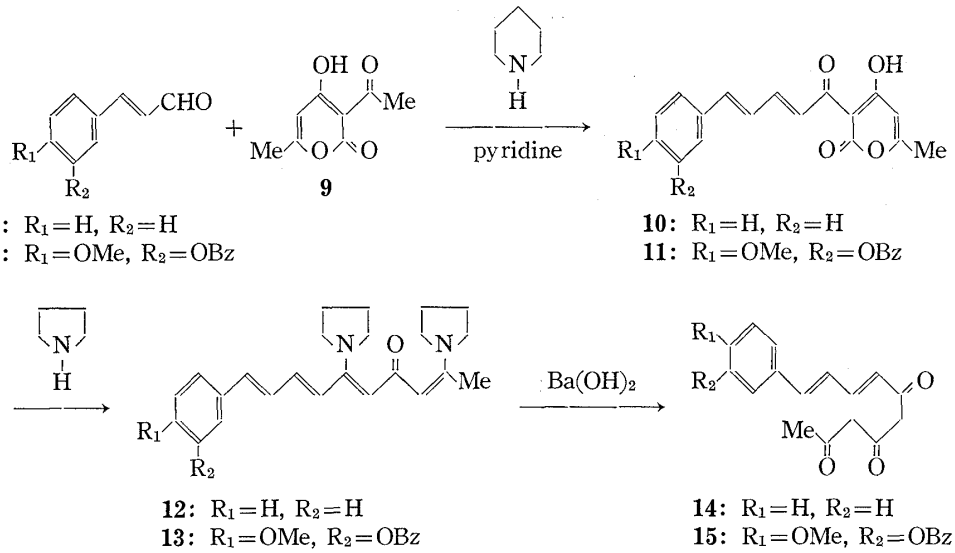


Chart 3

180.5°. The conversion of the 2-pyrone **11** to the triketone **15** by acid hydrolysis followed by treatment with aq. $Ba(OH)_2$ as described on the preceding report[2] occurred, but only afforded the undesired debenzylated product. Therefore, a new method for the conversion from **11** to **15** was required. As a preliminary experiment, the simple 2-pyrone **10** was transformed into the dienaminoketone **12** (62.6% yield), mp 184.5—185.5°, by heating at 100° with pyrrolidine (2 equiv.) in toluene. The enaminoketone **12** afforded the corresponding β-triketone **14** (94.3% yield), mp 135—136.5°, upon hydrolysis with aq. $Ba(OH)_2$. On similar

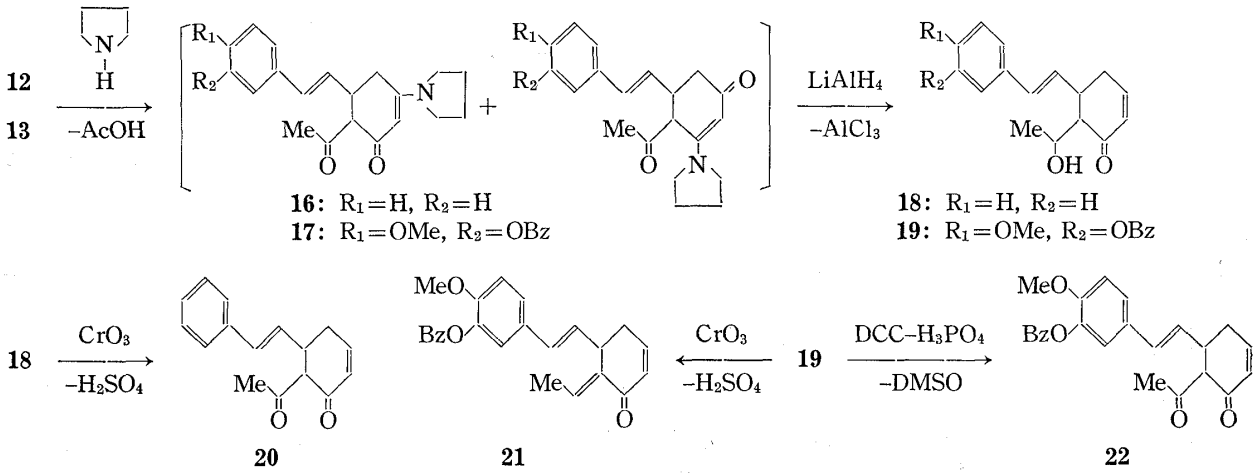
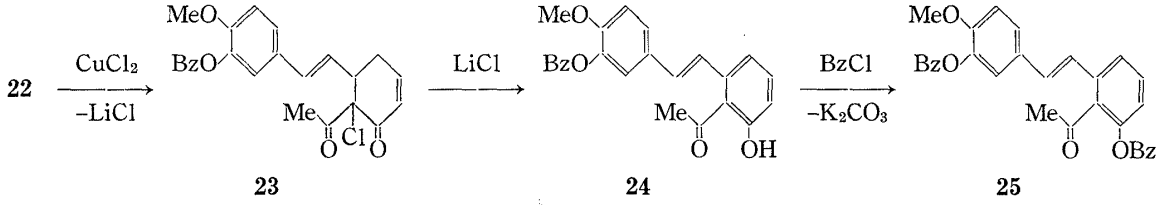


Chart 4

treatment, the 3,4-disubstituted 2-pyrone **11** gave the enaminoketone **13** (68.8% yield), mp 152—153.5°, which was subsequently transformed into the triketone **15** (89% yield), mp 140—142°.

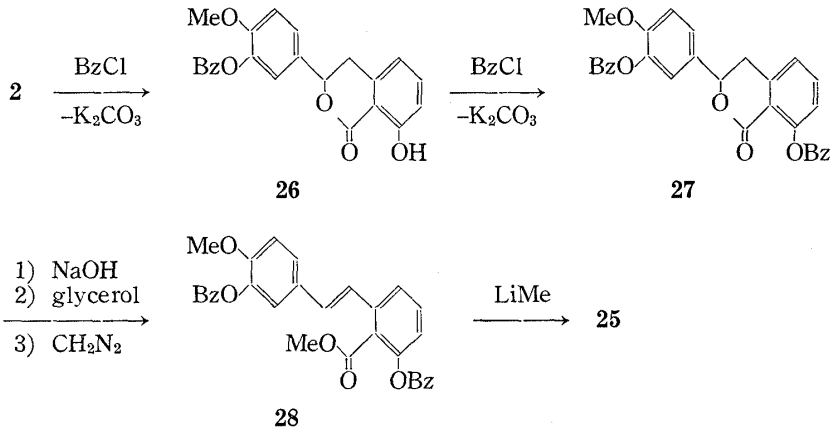
Although several attempts at intramolecular Michael-type condensation of **15** were unsuccessful, the enaminoketone **12** gave the cyclized enaminoketone mixture **16** when treated with a mixture of acetic acid-pyrrolidine in ethanol-H_2O (10 : 1) under reflux. The resulting mixture **16**, without separation, was reduced with $LiAlH_4$-$AlCl_3$ to yield **18**, which was oxidized with Jones' reagent to yield the diketone **20**, mp 98.5—99.5°. Similarly, the 3,4-disubstituted enaminoketone **13** gave the cyclized enaminoketone **17**, which was reduced without separation to give **19** and oxidized under Pfitzner–Moffatt[7] oxidation conditions with dicyclohexylcarbodiimide-H_3PO_4 in DMSO to afford the expected diketone **22**, mp 118—119.5°,[8] in an overall yield from **13** of 8.2%.



23 **24** **25**

Chart 5

The diketone **22** gave the chloride **23** (95.5% yield) by the chlorination with $CuCl_2 \cdot 2H_2O$–LiCl in DMF, followed by dehydrochlorination with LiCl in DMF to afford the stilbene **24** (71.3% yield).



26 **27** **28**

Chart 6

The structure of **24** was confirmed by direct comparison of the dibenzyl derivative **25** with an authentic sample synthesized from dibenzylphyllodulcin (**27**), mp 138—139.5°, by conversion to the corresponding ester **28**, mp 84.5—85.5° (starting from the sodium salt of **27** in glycerol and methylating with diazomethane), followed by reaction with MeLi to afforded **25**, as shown in Chart 6. This compound **25** was identical with the dibenzyl derivative **25** of stilbene synthesized from the enaminoketone **13**.

Finally, the dihydroxy-stilbene **29**, mp 104—105°, obtained by acid hydrolysis of **24**, was oxidized to the acid **30** by transformation to the pyridinium salt by reaction with pyridine and

7) J.D. Albright and L. Goldman, *J. Org. Chem.*, **30**, 1107 (1965). W.W. Epstein, and F.W. Sweet, *Chem. Rev.*, **67**, 247 (1967).

8) Oxidation of **19** with Jones' reagent yielded only a dehydration product **21**.

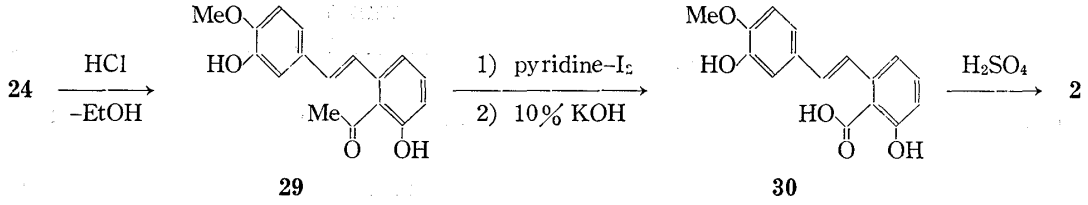


Chart 7

iodine, followed by hydrolysis with aq. KOH.[9] The acid **30** was treated with cold conc. H_2SO_4 without purification to afford the dihydroisocoumarin, (±)-phyllodulcin (**2**), mp 128—130°. The synthetic isocoumarin was identical with natural phyllodulcin.

Experimental[10]

3-Benzyloxy-4-methoxybenzaldehydediethyl Acetal (5)——Ethylorthoformate (3.36 g) and NH_4Cl (0.04 g) were added to a solution of benzylisovanillin **4** (5 g) in ethanol (3 ml), and the mixture was refluxed for 3 hr. The reaction mixture was concentrated under a vacuum, poured into ice-water and extracted with ether. The ether layer was dried and concentrated. The residue was recrystallized from ether–*n*-hexane to yield 6.05 g (92.6%) of **5** as colorless crystals, mp 44.5—45.5°. IR ν_{max}^{Nujol} cm^{-1}: 1605, 1590, and 1513. NMR ($CDCl_3$) δ: 1.20 (6H, t, J=6.4 Hz, $-OCH_2CH_3\times2$), 3.57 (4H, q, J=6.4 Hz, $-OCH_2CH_3\times2$), 3.92 (3H, s, $-OCH_3$), 5.23 (2H, s, $-OCH_2-$), 5.48 (1H, s, $-CH(-O-)_2$), and 7.03—7.70 (8H, m, aromatic H×8).

3-(3-Benzyloxy-4-methoxyphenyl)-3-ethoxypropionaldehydediethyl Acetal (6)——A solution (0.2 ml) of 10% $ZnCl_2$ in ethyl acetate was added to a mixture of **5** (3.16 g) and ethylvinylether (0.8 g), and the whole was refluxed at 40—45° for 3 hr. The reaction mixture was poured into ice-water and then extracted with ether. The ether layer was washed with sat. $NaHCO_3$, dried and concentrated. The residue was distilled to give 2.6 g (67%) of **6** as an oil, bp 175—185°/0.8 mmHg. IR $\nu_{max}^{liq.}$ cm^{-1}: 1612, 1600, and 1512. NMR ($CDCl_3$) δ: 0.93—1.30 (9H, m, $-CH_3\times3$), 1.90 (2H, m, $-CH_2-$), 3.08—3.67 (6H, m, $-OCH_2-\times3$), 3.90 (3H, s, $-OCH_3$), 4.12—4.70 (2H, m, $-CH(-O-)_2$ and ϕ-CH–O–), 5.20 (2H, s, $-OCH_2-$), 6.95 (3H, m, aromatic H×3), and 7.50 (5H, m, aromatic H×5).

3-(3-Benzyloxy-4-methoxyphenyl)-2-propenal (7)——H_2O (130 ml), 85% H_3PO_4 (30 ml) and hydroquinone (1 g) were added to a solution of **6** (58.4 g) in dioxane (430 ml), and the whole was heated overnight at 100° under a nitrogen atmosphere. The reaction mixture was concentrated under a vacuum, made basic with sat. $NaHCO_3$ and extracted with ether. The ether layer was washed with H_2O, dried and concentrated. The residue was recrystallized from ether to yield 24 g (59.6%) of **7** as crystals, mp 83—83.5°. *Anal.* Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.18; H, 6.03. MS *m/e*: 268 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1665, 1620, 1595, and 1515. NMR ($CDCl_3$) δ: 3.98 (3H, s, $-OCH_3$), 5.24 (2H, s, $-OCH_2-$), 6.60 (1H, q, J=7.6 Hz, J=16 Hz, olefinic H), 7.50 (5H, m, aromatic H×5), and 9.77 (1H, d, J=7.6 Hz, –CHO).

3-[5-(3-Benzyloxy-4-methoxyphenyl)-2.4-pentadienoyl]-4-hydroxy-6-methyl-2H-2-pyranone (11)——A mixture of **7** (1 g), dehydroacetic acid **9** (1 g) and piperidine (0.2 ml) in dry pyridine (1.8 ml) was heated on a water bath for 0.5 min and then left to stand at room temperature. The separated crystals were collected and recrystallized from chloroform–ethanol to yield 1.4 g (89.7%) of **11** as red crystals, mp 179—180.5°. *Anal.* Calcd for $C_{25}H_{22}O_6$: C, 71.76; H, 5.30. Found: C, 71.66; H, 5.37. MS *m/e*: 418 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1720, 1643, 1613, 1598, and 1512. NMR ($CDCl_3$) δ: 2.23 (3H, s, $-CH_3$), 3.90 (3H, s, $-OCH_3$), 5.18 (2H, s, $-OCH_2-$), 5.93 (1H, s, olefinic H), and 7.43 (5H, m, aromatic H×5).

4-Hydroxy-6-methyl-3-(5-phenyl-2,4-pentadienoyl)-2H-2-pyranone (10)——**10** was prepared from *trans*-cinnamaldehyde (**8**) and dehydroacetic acid (**9**).[2]

10-Phenyl-2,6-dipyrrolidino-2,5,7,9-decatetraen-4-one (12)——Pyrrolidine (15 g) was added to a solution of **10** (26 g) in toluene (70 ml), heated on a water bath for 0.5 min and allowed to stand at room temperature. The separated crystals were collected and recrystallized from ethanol to yield 21 g (62.6%) of **12** as orange-colored crystals, mp 184—185.5°. MS *m/e*: 362 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1595, and 1558. NMR ($CDCl_3$) δ: 1.98 (4H, m, $-CH_2CH_2-$), 2.58 (3H, s, $-CH_3$), 3.40 (4H, m, $-CH_2NCH_2-$), 4.75 (1H, s, olefinic H), 5.32 (1H, s, olefinic H), 6.03 (1H, d, J=14 Hz, olefinic H), and 7.40 (5H, m, aromatic H×5).

9) Oxidation of **24** and **25** by the method described did not afford the corresponding acids.

10) All melting points are uncorrected. IR spectra were recorded with a Hitachi 215 spectrometer, UV spectra with a Hitachi 124 spectrometer, NMR spectra with a Varian T-60 spectrometer with tetramethylsilane as an internal standard ($CDCl_3$ soln.), and MS spectra 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 TLC, respectively.

10-Phenyl-7,9-decadiene-2,4,6-trione (**14**)——A saturated aqueous solution of $Ba(OH)_2$ (3.4 g) was added to a solution of **12** (6 g) in ethanol (60 ml), and the whole was refluxed on a water bath for 30 min. The precipitated Ba salts were separated from the solution by filtration, acidified with 10% HCl and extracted with chloroform. The organic layer was washed with H_2O, dried and concentrated. The residue was recrystallized from chloroform–ether to yield 4.0 g (94.3%) of **14** as yellow crystals, mp 135—136.5°. The compound **14** was identical with an independently synthesized authentic sample.[2]

10-(3-Benzyloxy-4-methoxyphenyl)-2,6-dipyrrolidino-2,5,7,9-decatetraen-4-one (**13**)——A solution of **11** (500 mg) in toluene (1 ml) was heated on a water bath for 0.5 min with pyrrolidine (200 mg) and then the mixture was allowed to stand at room temperature. The separated crystals were collected and recrystallized from chloroform–ethanol to yield 400 mg (68.8%) of **13** as orange-colored crystals, mp 152—153.5°. MS *m/e*: 498 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1512. NMR ($CDCl_3$) δ: 1.94 (4H, m, $-CH_2CH_2-$), 2.56 (3H, s, $-CH_3$), 3.37 (4H, m, $-CH_2NCH_2-$), 3.88 (3H, s, $-OCH_3$), 4.74 (1H, s, olefinic H), 5.17 (2H, s, $-OCH_2-$), 5.30 (1H, s, olefinic H), 5.97 (1H, d, $J=14$ Hz, olefinic H), and 7.44 (5H, m, aromatic H×5).

10-(3-Benzyloxy-4-methoxyphenyl)-7,9-decadiene-2,4,6-trione (**15**)——A saturated aqueous solution of $Ba(OH)_2$ (0.5 g) was added to a solution of **13** (1 g) in ethanol (10 ml), and the whole was refluxed on a water bath for 30 min. The precipitated Ba salts were separated by filtration, acidified with 10% HCl and then extracted with chloroform. The organic layer was washed with H_2O, dried and concentrated. The residue was recrystallized from chloroform–ethanol to yield 700 mg (89%) of **15** as yellow crystals, mp 140—142°. *Anal.* Calcd for $C_{24}H_{24}O_5$: C, 73.45; H, 6.16. Found: C, 73.26; H, 6.16. IR ν_{max}^{Nujol} cm^{-1}: 1622, 1595, 1570, and 1517.

The Mixture 16——A mixture of **12** (15 g), H_2O (60 ml) in ethanol (540 ml), acetic acid (0.7 g) and pyrrolidine (0.85 g) was refluxed overnight. The reaction mixture was concentrated under a vacuum, poured into ice-water and extracted with chloroform. The organic layer was washed with 10% HCl and sat. $NaHCO_3$, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate yielded 4.5 g (35%) of **16** as an oil, giving two spots on TLC. The mixture **16** was used in the next step without separation.

6-(1-Hydroxyethyl)-5-styryl-2-cyclohexenone (**18**)——A solution of $AlCl_3$ (0.67 g) in THF (4 ml) was added at 0° to a solution of $LiAlH_4$ (0.7 g) in THF (18 ml), and the whole was stirred at 0° for 1 hr. A solution of the mixture **16** (1 g) in THF (5 ml) was then added and the reaction mixture was stirred overnight at 0°. The reaction mixture was poured into ice-water, acidified with 10% HCl and extracted with chloroform. The organic layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 0.36 g (46%) of **18** as an oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 1664. NMR ($CDCl_3$) δ: 1.22 (3H, d, $J=6.4$ Hz, $-CH_3$), 3.90 (1H, m, =CH–O–), and 7.27 (5H, s, aromatic H×5).

6-Acetyl-5-styryl-2-cyclohexenone (**20**)——A solution of **18** (121 mg) in acetone (5 ml) was treated with 0.5 ml of Jones' reagent [prepared by adding 6 ml of H_2O to a mixture of CrO_3 (2.67 g) and conc. H_2SO_4 (2.3 ml)], and the whole was allowed to stand at room temperature for 15 min. The reaction mixture was poured into ice-water and then extracted with chloroform. The organic layer was washed with sat. $NaHCO_3$ and H_2O, dried and concentrated. The residue was recrystallized from ether–*n*-hexane to yield 91 mg (76%) of **20** as colorless crystals, mp 98.5—99.5°. The compound **20** was identical with an independently synthesized authentic sample.[2]

The Mixture 17——A mixture of **13** (498 mg), H_2O (3 ml) in ethanol (27 ml), acetic acid (70 mg) and pyrrolidine (85 mg) was refluxed overnight. The reaction mixture was concentrated under a vacuum, poured into ice-water and extracted with chloroform. The organic layer was washed with 10% HCl and sat. $NaHCO_3$, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate yielded 120 mg (27%) of the mixture **17** as an oil giving two spots on TLC. IR $\nu_{max}^{liq.}$ cm^{-1}: 1700, 1595, 1540, and 1505. NMR ($CDCl_3$) δ: 1.79 (4H, m, $-CH_2CH_2-$), 2.31 and 2.42 (3H, s×2, $-COCH_3$), 2.80 (2H, m, $-CH_2-$), 3.45 (4H, m, $-CH_2NCH_2-$), 3.88 and 3.94 (3H, s×2, $-OCH_3$), 5.11 (2H, s, $-OCH_2-$), and 7.40 (5H, m, aromatic H×5). The mixture **17** was used in the next step without separation.

5-[2-(3-Benzyloxy-4-methoxyphenyl)ethenyl]-6-(1-hydroxyethyl)-2-cyclohexenone (**19**)——A solution of $AlCl_3$ (534 mg) in THF (5 ml) was added to a solution of $LiAlH_4$ (454 mg) in THF (20 ml), at 0° and the mixture was stirred at 0° for 1 hr. A solution of **17** (1.1 g) in THF (4 ml) was then added and the whole was stirred overnight at 0°. The reaction mixture was poured into ice-water, acidified with 10% HCl and extracted with chloroform. The organic layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 350 mg (38.4 %) of **19** as an oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 1660, 1605, 1585, and 1518. NMR ($CDCl_3$) δ: 1.21 (3H, d, $J=4.4$ Hz, $-CH_3$), 3.85 (3H, s, $-OCH_3$), 5.14 (2H, s, $-OCH_2-$), and 7.37 (5H, m, aromatic H×5).

5-[2-(3-Benzyloxy-4-methoxyphenyl)ethenyl]-6-ethylidene-2-cyclohexenone (**21**)——A solution of **19** (170 mg) in acetone (4 ml) was treated with 5 drops of Jones' reagent (prepared as described above) and the mixture was allowed to stand at room temperature for 15 min. The reaction mixture was poured into ice-water and extracted with chloroform. The organic layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 104 mg (64%) of **21** as an oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 1680, 1600, and 1518. NMR ($CDCl_3$) δ: 1.47 (3H, d,

J=6 Hz, $-CH_3$), 3.94 (3H, s, $-OCH_3$), 5.18 (2H, s, $-OCH_2-$), and 7.37 (5H, m, aromatic H×5).

6-Acetyl-5-[2-(3-benzyloxy-4-methoxyphenyl)ethenyl]-2-cyclohexenone (22)——Crystalline orthophosphoric acid (30 mg) was added to a solution of **19** (115 mg) and DCC (190 mg) in dry DMSO (4.5 ml), and the whole was heated overnight at 60°. The mixture was cooled and poured into a mixture of H_2O (1 ml) in methanol (3 ml). After allowing the solution to stand at room temperature for 30 min, the resulting solid was removed by filtration and washed with aqueous methanol. The filtrate was diluted with H_2O, and extracted with ether. The ether layer was washed with sat. $NaHCO_3$, dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 90 mg (78.7%) of **22** as colorless crystals (ether–*n*-hexane), mp 118—119.5°. MS *m/e*: 376 (M^+). IR $\nu_{max}^{liq.}$ cm^{-1}: 1720, 1670, 1610, 1590, and 1520. NMR ($CDCl_3$) δ: 2.10 (3H, s, $-COCH_3$), 3.85 (3H, s, $-OCH_3$), 5.12 (2H, s, $-OCH_2-$), and 7.35 (5H, m, aromatic H×5).

6-Acetyl-5-[2-(3-benzyloxy-4-methoxyphenyl)ethenyl]-6-chloro-2-cyclohexenone (23)——A mixture of $CuCl_2 \cdot 2H_2O$ (250 mg), LiCl (25 mg) and DMF (3 ml) was heated at 80°, and then **22** (155 mg) was added and the whole was heated at 80° for 3 hr. The reaction mixture was poured into ice-water and extracted with ether. The ether layer was washed with 10% HCl, sat. $NaHCO_3$ and H_2O, then dried and concentrated to yield 162 mg (95.5%) of **23** as an oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 1710, 1690, 1605, 1595, and 1515. The compound **23** was used in the next step without further purification.

2-Acetyl-3-[2-(3-benzyloxy-4-methoxyphenyl)ethenyl]-phenol (24)——LiCl (50 mg) was added to a solution of **23** (162 mg) in DMF (5 ml), and the mixture was heated at 100° for 2 hr. The reaction mixture was poured into ice-water and extracted with ether. The ether layer was extracted with 10% NaOH. The aqueous layer was acidified with conc. HCl and then extracted with ether. The resulting ether layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 105 mg (71.3%) of **24** as a colorless oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 1630, 1600, 1590, and 1520. NMR ($CDCl_3$) δ: 2.52 (3H, s, $-COCH_3$), 3.92 (3H, s, $-OCH_3$), 5.18 (2H, s, $-OCH_2-$), 7.37 (5H, m, aromatic H×5), and 11.90 (1H, s, –OH).

2-Acetyl-3,3′-dibenzyloxy-4′-methoxystilbene (25)——Benzyl chloride (40 mg) was added to a solution of **24** (132 mg) and anhydrous K_2CO_3 (40 mg) in ethanol (4 ml), and the mixture was refluxed on a water bath for 4 hr. The reaction mixture was concentrated under a vacuum, poured into water and extracted with chloroform. The organic layer was washed with 10% KOH and 10% HCl, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 127 mg (77.6%) of **25** as colorless crystals (ether), mp 113.5—114.5°. *Anal.* Calcd for $C_{31}H_{28}O_4$: C, 80.15; H, 6.08. Found: C, 80.24; H, 6.13. MS *m/e*: 464 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1690, 1590, 1570, and 1520. NMR ($CDCl_3$) δ: 2.50 (3H, s, $-COCH_3$), 3.87 (3H, s, $-OCH_3$), 5.10 (2H, s, $-OCH_2-$), 5.18 (2H, s, $-OCH_2-$), and 7.38 (10H, m, aromatic H×10).

3-(3-Benzyloxy-4-methoxyphenyl)-3,4-dihydro-8-hydroxyisocoumarin (26)——Anhydrous K_2CO_3 (1 g) and benzyl chloride (1 g) were added to a solution of phyllodulcin **2** (2 g) in DMF (5 ml), and the mixture was heated at 90° for 4 hr with stirring. The reaction mixture was poured into ice-water and extracted with chloroform. The organic layer was washed with 10% HCl, dried and concentrated. The residue was washed with *n*-hexane and subjected to silica gel chromatography. The chloroform eluate gave 1.75 g (66.5%) of **26** as crystals (ethanol) mp 145—146°. *Anal.* Calcd for $C_{23}H_{20}O_5$: C, 73.39; H, 5.36. Found: C, 73.49; H, 5.36. MS *m/e*: 376 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1685, 1605, 1595, and 1520. NMR ($CDCl_3$) δ: 3.07 (2H, m, $-CH_2-$), 3.86 (3H, s, $-OCH_3$), 5.13 (2H, s, $-OCH_2-$), 5.46 (1H, q, J=6 Hz, J=12 Hz, –OCH=), 7.38 (5H, m, aromatic H×5), and 11.92 (1H, s, –OH).

8-Benzyloxy-3-(3-benzyloxy-4-methoxyphenyl)-3,4-dihydroisocoumarin (27)——Anhydrous K_2CO_3 (0.4 g) and benzyl chloride (0.4 g) were added to a solution of **26** (1 g) in DMF (3 ml), and the mixture was heated at 90° for 4 hr with stirring. The reaction mixture was poured into ice-water and extracted with chloroform. The organic layer was washed with 10% HCl, dried and concentrated. The residue was washed with *n*-hexane and subjected to silica gel chromatography. The chloroform eluate gave 0.72 g (58.1%) of **27** as crystals (ether–*n*-hexane), mp 138—139.5°. *Anal.* Calcd for $C_{30}H_{26}O_5$: C, 77.23; H, 5.62. Found: C, 77.16; H, 5.54. MS *m/e*: 466 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1727, 1600, 1580, and 1522. NMR ($CDCl_3$) δ: 3.00 (2H, m, $-CH_2-$), 3.85 (3H, s, $-OCH_3$), 5.12 (2H, s, $-OCH_2-$), 5.23 (2H, s, $-OCH_2-$), 5.30 (1H, q, J=6 Hz, J=12 Hz, –OCH=), and 7.37 (10H, m, aromatic H×10).

Methyl 2-Benzyloxy-6-[2-(3-benzyloxy-4-methoxyphenyl)ethenyl]benzoate (28)——A solution of **27** (223 mg) in ethanol (5 ml) was added to a solution of NaOH (30 mg) in H_2O (1 ml), then the mixture was refluxed on a water bath for 20 min and evaporated to dryness *in vacuo*. Absolute glycerol (4 ml) was added to the residue and the mixture was heated at 180° for 4 hr. The reaction mixture was then acidified with 10% HCl and extracted with chloroform. The organic layer was washed with H_2O and dried. A large excess of an ether solution of diazomethane was added to the chloroform solution and the whole was kept at room temperature for 15 min. The mixture was concentrated and the residue was subjected to silica gel chromatography. The chloroform eluate gave 88 mg (36.7%) of **28** as colorless crystals (ether–*n*-hexane), mp 84.5—85.5°. MS *m/e*: 480 (M^+). IR $\nu_{max}^{liq.}$ cm^{-1}: 1730, 1635, 1600, 1580, and 1520. NMR ($CDCl_3$) δ: 3.88 (6H, s, $-OCH_3$×2), 5.12 (2H, s, $-OCH_2-$), 5.18 (2H, s, $-OCH_2-$), and 7.37 (10H, m, aromatic H×10).

The Preparation of 25 from 28——Methyl iodide (14.2 g) was added to a mixture of Li (0.8 g) and absolute

ether (60 ml), and the mixture was stirred for 2 hr under nitrogen. **28** (1.2 g) was then added, and the whole was refluxed for 3 hr under nitrogen. The reaction mixture was acidified with 5% HCl and extracted with ether. The ether layer was washed with H_2O, dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 0.97 g (83.6%) of **25** as crystals (ether), mp 113.5—114.5°. This compound **25** was identical with the compound **25** previously described.

2-Acetyl-3-[2-(3-hydroxy-4-methoxyphenyl)ethenyl]phenol (**29**)——Conc. HCl (3 ml) was added to a solution of **24** (187 mg) in ethanol (5 ml), and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with H_2O and extracted with chloroform. The organic layer was dried and concentrated. The residue was subjected to silica gel chromatography. The first chloroform eluate gave 65.5 mg (35%) of **24** as an oil. The second chloroform eluate gave 45.5 mg (32%) of **29** as crystals (ether–*n*-hexane) mp 104—105°. MS *m/e*: 284 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1620, 1585, and 1515. NMR ($CDCl_3$) δ: 2.59 (3H, s, $-COCH_3$), 3.81 (3H, s, $-OCH_3$), and 11.93 (1H, m, –OH).

6-[2-(3-Hydroxy-4-methoxyphenyl)ethenyl]salicylic Acid (**30**)——I_2 (85 mg) was added to a solution of **29** (142 mg) in pyridine (250 mg). The mixture was heated on a water bath for 1 hr and then allowed to stand at room temperature. The separated crystals were collected, added to a mixture of ethanol and 10% KOH (3 ml), and heated on a water bath for 1 hr. The reaction mixture was acidified with 10% HCl and extracted with ethyl acetate. The organic layer was extracted with sat. $NaHCO_3$. The aqueous layer was acidified with conc. HCl and extracted with ethyl acetate. The resulting organic layer was dried and concentrated to yield 40 mg (28%) of **30**. The compound **30** was used in the next step without further purification.

(±)-**Phyllodulcin** (**2**)——Compound **30** (71 mg) was added to conc. H_2SO_4 (1 ml) and stirred at 0° for 5 min. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with sat. $NaHCO_3$, dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 31.2 mg (44%) of **2** as crystals (ether–*n*-hexane), mp 128—130°. IR ν_{max}^{KBr} cm^{-1}: 1670, 1620, 1590, and 1518. NMR ($CDCl_3$+DMSO-d_6) δ: 3.13 (2H, m, $-CH_2-$), 3.83 (3H, s, $-OCH_3$), 5.46 (1H, q, $J=5$ Hz, $J=11$ Hz, –OCH=), and 10.48 (1H, s, –OH). This compound **2** was identical with natural (±)-phyllodulcin.