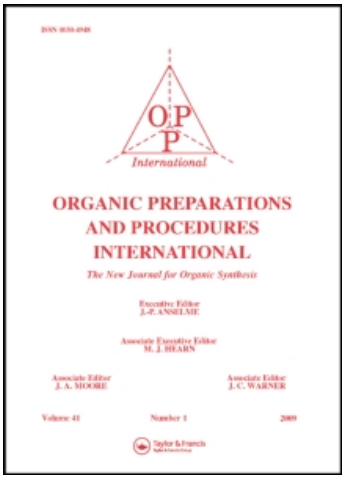

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THE TOTAL SYNTHESIS OF DL-PHYLLODULCIN†

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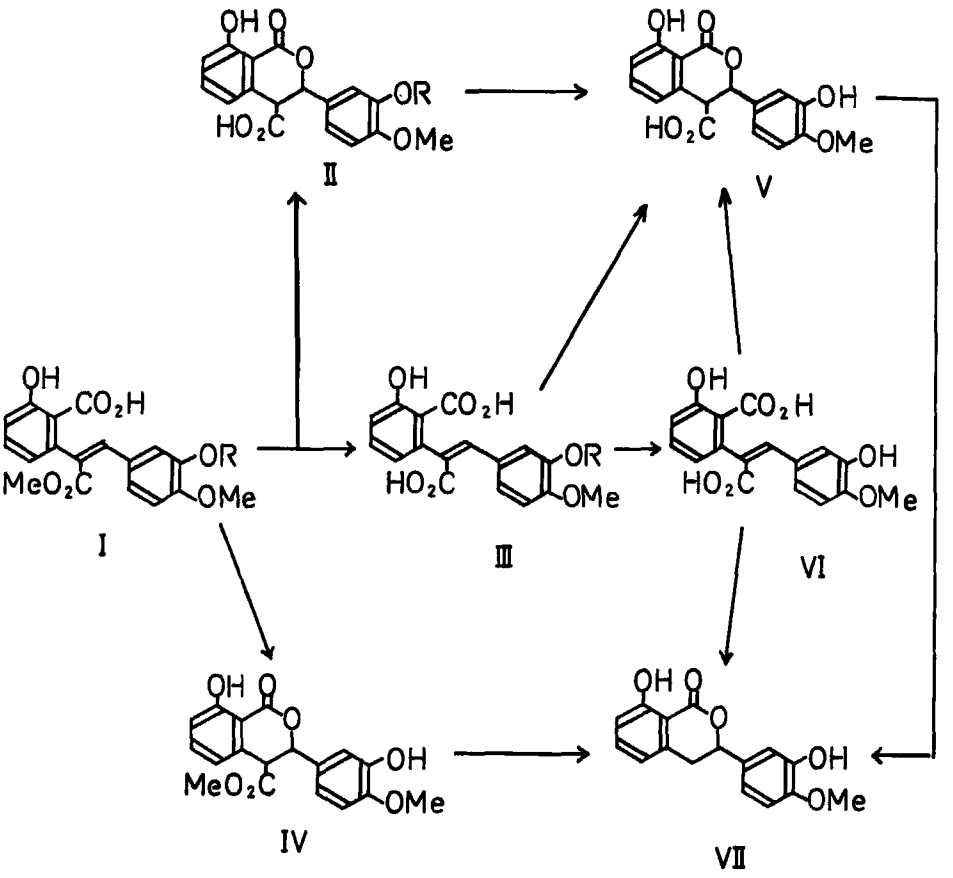
D-Phyllodulcin (VII)[1] was first isolated as a sweetening component in Hydrangea serrata seringe var thunbergii Sugimoto (Japanese name: Amacha) and shown to contain the dihydroisocoumarin skeleton by Asahina and Asano;[2] its absolute configuration was determined by Arakawa.[3,4] We have developed a practical route to DL-8-desoxyphyllodulcin[5] and successfully applied it to the total synthesis of DL-phyllodulcin.

Half ester I was isolated in 80-90% yield and identified as the dicarboxylic acid III by alkaline hydrolysis; in addition, a 10% yield of 3,4-dihydroisocoumarin (II)[6] was isolated from the mother liquor of recrystallization. Compound IV was obtained smoothly in 85% yield by bubbling hydrogen bromide into a chloroform solution of I for 4 hrs with concomitant debenzylation.[7] Treatment of IV with $AlBr_3$ in aqueous solution at 110-125° in an autoclave gave DL-phyllodulcin (VII)[2] in 17% yield. Alternatively, base-

catalyzed hydrolysis of I gave a 90% yield of III which could be debenzylated to VI with hydrogen bromide in chloro-



form followed by cyclization in a separate step to V (70% yield). Diacid III could also be cyclized and debenzylated in one step to V with hydrogen bromide in acetic acid in 70% yield. Heating an aqueous solution of V or VI at 140° in an autoclave gave DL-phyllodulcin (VII) in 60% yield; the by-products were 3-hydroxyhomophthalic acid and isovanillin.

The conformation of DL-phyllodulcin was ascertained by its NMR spectra (Fig. 1). The 3-aryl group of phyllodulcin

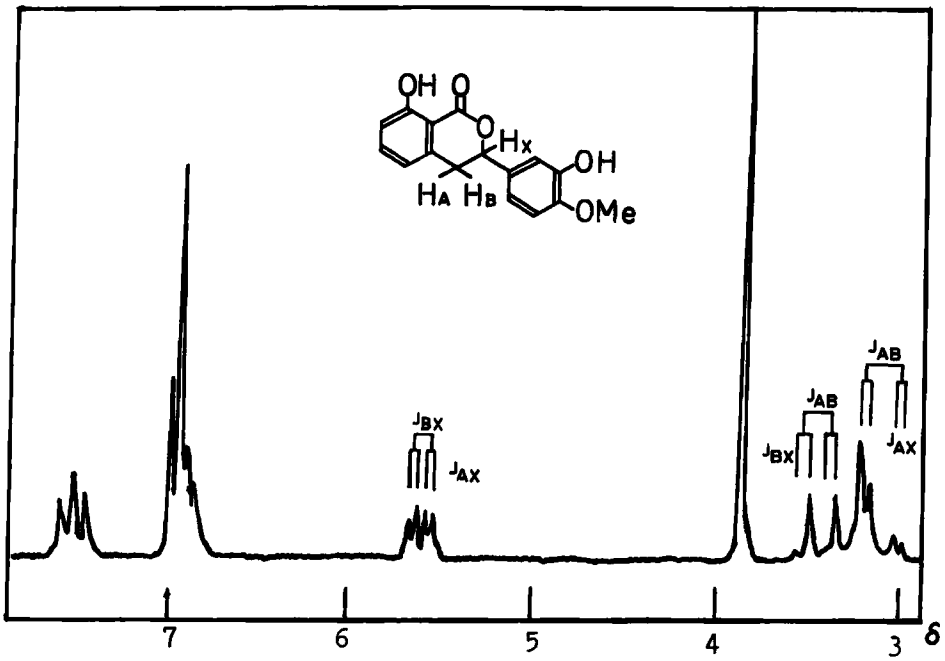


Fig. 1. NMR spectrum of DL-phyllodulcin

was assigned the equatorial position on the basis of the magnitude of the coupling constants between H_3 and the two hydrogens at C-4. The observed values J_{AX} = 5 Hz and J_{BX} = 8-9 Hz are consistent with a dihedral angle of 40° (H_3 and H_4) and 190° (H_3 and $H_{4'}$) as shown by Dreiding models.

EXPERIMENTAL

All mps are uncorrected. IR spectra were obtained as KBr pellets on a Nippon Bunko Model IR-G; UV spectra were determined on a Hitachi Spectrophotometer Model EPS-3T; NMR spectra were measured on a Hitachi-Perkin Elmer Model R-20A in d_6-DMSO; Mass spectra were determined on a Hitachi Model RMS4. Elemental analyses were performed with a Perkin Elmer 240 Analyzer. Thin layer chromatographic (TLC) results

were obtained using Spotfilm of Silicagel f (Tokyo Kasei Co., Ltd.). Solvent system was toluene:ethyl formate:formic acid (5:4:1).

3-(3'-Benzyloxy-4'-methoxyphenyl)-4-carboxy-8-hydroxy-3,4-dihydroisocoumarin (II) and 2-carboxy-3-hydroxy-3'-benzyloxy-4'-methoxy-α-carboxy stilbene (III). - After the Stobbe condensation,[5] 2N NaOH solution was added to a benzene solution of the reaction mixture. This solution was heated to reflux for 3 hrs and was acidified with 6N HCl solution to give pale yellow crystals (III), which were recrystallized from methanol in 80-90% yield, mp. 197° (dec.).

Anal. Calcd. for $C_{24}H_{20}O_7$: C, 68.56; H, 4.80.
Found: C, 68.68; H, 4.82.

TLC, R_f = 0.44.

From the mother liquor which had stood overnight, white crystals (II) were obtained in 10% yield, mp. 207-208° (dec.).

Anal. Calcd. for $C_{24}H_{20}O_7$: C, 68.56; H, 4.80.
Found: C, 68.76; H, 4.69.

IR: $\nu_{C=O}$ = 1670 cm^{-1} (lactone carbonyl); NMR bands (d_6-DMSO) at δ = 5.95 (H_3, d, J = 3-4 Hz), δ = 4.26 (H_4, d, J = 3-4 Hz).

2-Carboxy-3,3'-dihydroxy-4'-methoxy-α-carboxy stilbene (VI).- Two grams of hydrogen bromide (0.025 mole) and 5 g. (0.012 mole) of III were dissolved in 100 ml of chloroform in a sealed tube, and stirred for 4 hrs at room temperature to give 3.5 g. (88%) of white crystals of VI, mp. 216-217°.

Anal. Calcd. for $C_{17}H_{14}O_7$: C, 61.82; H, 4.27.
Found: C, 62.07; H, 4.45.

IR; ν = 3500 cm^{-1} (-OH), $\nu_{C=O}$ = 1660 cm^{-1} (acid carbonyl);

NMR bands (d_6-DMSO) at δ = 6.5 (vinyl proton, s); TLC, Rf = 0.41.

3-(3'-Hydroxy-4'-methoxyphenyl)-4-carbomethoxy-8-hydroxy-3,4-dihydroisocoumarin (IV).- Gaseous hydrogen bromide was bubbled for 4 hrs. through a solution of 10 g. (0.023 mole) of I in 100 ml. of chloroform kept at 30°. The reaction mixture was then evaporated in vacuo to give a residue, which was treated with 50-100 ml of ether and allowed to stand overnight. The white precipitate was filtered and washed twice with ether. Recrystallization from ethanol gave 6.3 g. (80%) of white needles of IV, mp. 130.5-131.5°.

Anal. Calcd. for $C_{18}H_{16}O_7$: C, 62.79; H, 4.68
Found: C, 62.32; H, 4.60

IR: $\nu_{C=O}$ = 1735 cm^{-1} (ester carbonyl), 1670 cm^{-1} (lactone carbonyl); NMR bands (d_6-DMSO) at δ = 5.86 (H_3, d), 4.46 (H_4, d), J = 7 Hz; TLC, Rf = 0.56

3-(3'-Hydroxy-4'-methoxyphenyl)-4-carboxy-3,4-dihydroisocoumarin (V). - a) From III. Forty grams (0.095 mole) of III and 15.4 g. (0.19 mole) of hydrogen bromide were dissolved in 340 g. of acetic acid in sealed tube, and stirred for 10 hrs at 50°. The reaction mixture was evaporated in vacuo to give a residue which was treated with 50 ml of ether and allowed to stand overnight to give V in 80% yield (25 g.). Recrystallization from acetic acid gave white plates, mp. 131-132° (dec.).

Anal. Calcd. for $C_{17}H_{14}O_7$: C, 61.82; H, 4.27
Found: C, 61.74; H, 4.31

IR; ν = 3370 cm^{-1} (-OH), $\nu_{C=O}$ = 1700 cm^{-1} (acid carbonyl),

1680 cm^{-1} (lactone carbonyl); NMR bands (d_6-DMSO) at δ = 5.84 (H_3, d), 4.45 (H_4, d), J = 7 Hz; TLC, Rf = 0.48.

b) From VI. Thirty-three grams (0.1 mole) of VI and 16.2 g. (0.2 mole) of hydrogen bromide were dissolved in 570 g. of acetic acid in a sealed tube and stirred for 10 hrs at 50°. The reaction mixture was evaporated in vacuo to give a residue which was treated with 80 ml of ether and allowed to stand overnight to give 27 g. (80%) of pale yellow crystals (V). Recrystallization from acetic acid gave white needles, mp. 131-132° (dec.).

DL-Phyllodulcin (VII). - a) From IV. Compound IV (8.2 g., 0.024 mole) and 6.4 g. (0.024 mole) of $AlBr_3$ and 300 ml of water were mixed in an autoclave and heated at 110-125° for 7 hrs. The reaction mixture was basified with NaOH to pH 10-11 and then neutralized to pH 6.8 with CO_2 gas to give 1.2 g. (17%) of phyllodulcin (VII). Recrystallization from ethanol gave white needles, mp. 130-132°.

Anal. Calcd. for $C_{16}H_{14}O_5$: C, 67.12; H, 4.93
Found: C, 67.25; H, 4.87

IR; ν = 3300 cm^{-1} (OH), $\nu_{C=O}$ = 1670 cm^{-1} (lactone carbonyl); NMR bands (d_6-DMSO) at δ = 5.60 (H_3, q), 3.25 (H_4, o), J_{AB} = 15-16 Hz, J_{AX} = 5 Hz, J_{BX} = 8-9 Hz; UV, λ_{max}^{EtOH} = 216 mμ (ε = 24800), 287 mμ (ε = 4147), 315 mμ (ε = 5028); TLC, Rf = 0.60. Molecular ion m/e value: 286 (M^+).

b) From V. Fourteen grams (0.042 mole) of V and 280 g. of water were mixed in an autoclave and heated at 140° for 4 hrs. The reaction mixture was extracted with 300 ml of chloroform and the solvent evaporated in vacuo to give crude

DL-phyllodulcin. Recrystallization from ethanol gave 5.7 g. of white needles of DL-phyllodulcin (47%).

c) From VI. Fourteen grams (0.042 mole) of VI and 125 g. of water were mixed in an autoclave and heated at 140° for 4 hrs. The reaction mixture was extracted with 200 ml of chloroform and evaporated in vacuo to give crude DL-phyllo dulcin. Recrystallization from ethanol gave 6.3 g. of white needles of DL-phyllodulcin (52%).

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* Author to whom correspondence and inquiries should be addressed.

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